A COMPARATIVE STUDY OF PHARMACO DYNAMIC EFFECTS OF ATRACURIUM AND VECURONIUM ADMINISTERED BY INTERMITTENT BOLUS AND CONTINUOUS INFUSION TECHNIQUES

THESIS

FOR

DOCTOR OF MEDICINE

(ANAESTHESIOLOGY)

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JHANSI (U. P.)

NISHEET AGGARWAL

Certificate

This is to certify that the work entitled "A Comparative Study Of Pharmacodynamic Effects Of Atracurium And Vecuronium Administered By Intermittent Bolus And Continuous Infusion Techniques" which is being submitted as a thesis for M.D. (Anaesthesiology), was conducted by Dr. Nisheet Aggarwal, himself in the department of Anaesthesiology, MLB Medical College, Jhansi.

The candidate has fulfilled the necessary stay in the department according to the regulations of the university.

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The techniques and methods described were undertaken by the candidate himself and the observations recorded, have periodically been checked by me from time to time.

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Introduction

INTRODUCTION

"Gentlemen, this is no humbug" , was the remark of Dr. John Collins Warren, the professosr of Surgery, when a second year student, WTG Morton, had made clinical trial of Ether on Friday 16th Oct. 1846, using a hastily devised glass reservoir incorporating the draw over principle of vaporization, and anaesthetized Edward Gilbert Abbott, a Young printer, while Warren deftly ligated congenital venous malformation in the left cervical triangle in Massachusetts General, Hospital,U.S.A..

Dr. Henry J.Higelow declared, "I have seen something today, which will go around the earth". Prior to this, nobody had ever dared to use ether in this way but Morton's youthful recklessness and disregard for the status quo convinced the world, and the idea became the sustained practice.

Morton died on 15th July 1868. The inscription on his memorial is "Inventor and revealer of anaesthetic inhalation, by whom pain in surgery was averted and anulled, before whom in all times surgery was agony, since whom, science has control of pain".

Yes, before Morton, surgery was in all times a classic agony and personified torture. Sugreons skill and craft centered around "bold strokes at lightening speed".

Initially, the main objectives of anaesthesia, viz, relief of pain, unawareness and muscular relaxation or paralysis to permit various surgical manipulations were achieved with increasing doses of a single drug like Ether, Chloroform, Trichlorethylene, Cyclopropane and Nitrous oxide in oxygen, but each drug had its advantages as well as dangerous hazards. The worst aspect of single drug anaesthesia was the high rapidly

administered dose to achieve all the three objectives resulting in prolonged elimination and post anaesthetic complications.

Induction with ether anaesthesia was often prolonged and stormy when compared to smooth but highly dangerous chloroform anaesthesia, occasionally precipitating death from fibrillation of heart during induction and from yellow atrophy of liver in late chloroform poisoning.

After a gestational period of 100 years, modern anaesthesia began around the 1940s. Intravenous anaesthetic thiopentone sodium introduced by *J.S. Lundy* of Rochester in 1934 was held responsible for infamous Pearl Harbour tragedy, killing more victims than Japanese bomb but soon realization of appropriately reduced doses in shock and other clinical situations, restored the useful status of this unique, smooth, dependable and most widely used agent even today. *Lundy* coined the term "Balanced Anaesthesia" to discribe his use of short acting barbiturates in conjunction with general or regional anaesthesia. This practice was further advanced when *Laborit and Huguenard* of France during the French Indo-China warfare of the late 1940s used a 'lytic cocktail' to prevent development of circulatory shock in the wounded patients. The resulting 'artificial hibernation' induced by simultaneous inj. of a barbiturate an analgesic and a tranquillizer was typified by a state of stress free, suspended animation. Actually this was the time when there was a move from the use of single drug therapy to the multidrug therapy, and a specific drug was used for a specific purpose i.e. simultaneous use of a sedative, muscle relaxant and an analgesic to provide a very smooth and quick induction, good muscle relaxation, complete abotition of awareness during the operative period and quick postoperative recovery. This concept not only provided excellent operative conditions but also led to further developments in the anaesthetic practice. As a result of muscle pa-

ralysis produced by muscle relaxants, need to control ventilation led to the development of mechanical ventilators, studies on the central and peripheral respiration were made and the concept of post - anaesthetic care units was introduced into the clinical practice.

During the subsequent years, the use of muscle relaxants had become a vitally inportant aspect of anaesthetic practice. The first use of muscle relaxant was the use of an alkaloid, which was a curare product derived from Chondrodendron Tomentosum by *Griffith & Johnson of Montreal* in 1942. But it was later noticed that it had disavantages of its own which included hypotension due to histamine release, anaphylactoid reactions, and cumulation after repetitive dosages. More over, to get an alkaloid in a large bulk was also a problem.

So the hunt was on for the development of synthetic and semisynthetic substances for providing muscle relaxation.

In 1947, Bovet described first synthetic muscle relaxant **Gallamine** but its use was found to be associated with tachycardia. Another major problem with Gallamine was its entire excretion by kidneys, which limited its use in patients with compromised cardiovascular and renal functions.

In 1949, Decamethonium was introduced by *Organ, Zaimis and Paton*, but subsequently it was found that it readily caused development of phase II block in repeated doses. Introduction of Succinyl Choline by *Thesleff and Foldes* et. al. in 1951 revolutionized anaesthetic practice by providing intense blockade of early onset and short duration, thereby greatly easing the maneuver of tracheal intubation.

Over next few decades, many newer agents were introduced into the practice that included Fazadinium bromide, Alcuronium and Pancuronium but all the agents had some side-effects. Out of these, only pancuronium which was introduced in 1967, could gain wide spread popularity but because of its cumulative property, pancurouium was not found to be very safe during prolonged duration of surgery and during infusions.

Thus, todate, numerous muscle relaxants have been introduced into the clinical practice but none has so far been able to fulfil the required standards of an ideal muscle relaxant, which are to mention a few-early onset, prolonged duration of action, rapid recovery, no dependence on liver and kindey for their elimination, no organ specific side-effects, no histamine release and no cumulation.

The simultaneous introduction of two muscle relaxants with intermediate duration of action i.e. Atracurium and Vecuronium in the early 1980s, although not ideal but considered to be near ideal,further revolutionized clinical anaesthesia by providing excellent muscluar relaxation, faster onset, a more rapid and measurable recovery of residual block than in the case of longer acting agents. This development -

(1) encouraged tracheal intubation by the use of nondepolarizing relaxants.

(2) made it more convinient to provide paralysis by continuous infusion.

(3) facilitated measurably improved post-operative neuro-muscular function

The virtual lack of cardiovascular effects of vecuronium over a very wide dose range established a bench mark for other relaxants, while the degradation of Atracurium via the chemical mechanism of "Hofmann elimination" curtailed any important influence of biochemical abnormalities on its pattern of blockade.

The first mention of the use of muscle relaxants by continuous infusion is of suxamethonium, but because of reports of development of phase II block and delay in recovery, its use was soon abondoned. Earlier, non depolarizer muscle relaxants were not used by infusion technique for the fear of their cumulative property and high incidence of post-operative recurarization.

Since both Atracurium and Vecuronium have been shown to possess no cumulative property *(Noelge G., Hinsken H., Buzello W., 1984)* and cardiovascular side effects *(Booij et al. 1980, Payne & Hughes 1981).* Hence these drugs have been advocated to be used by continuous infusions rather than in intermittent bolus doses, in order to obtain a consistent and near total paralysis of muscle through out surgery, particularly of longer duration.

Therefore, considering all these properties of Vecuronium and Atracurium, the present study was aimed -

(1) to evaluate the efficacy of continuous infusions of Atracurium and Vecuronium in producing consistent neuro-muscular blockade throughout the surgery.

(2) to observe, if there was any delay in recovery after the cessation of such infusions.

(3) to compare continuous infusion method with intermittent bolus doses, to provide a consistent neuromuscular blockade and rapid recovery.

(4) To evaluate the cardiovascular stability and any side effects during either techniques.

Review of Literature

REVIEW OF LITERATURE

Since birth, every man is fighting constantly to conquer the battle against physical pain. In the dark ages, memorable battles against pain were fought without much success. Prior to 1842, an operative procedure was a struggle for surgeon and an ordeal for the patient.

In January 1842, *Crawford W. Long* adminstered ether vapour to James in Jefferson Georgia but when the neighbours threatened to lynch him, he abandoned the technique and left the place.

Friday 16, Oct. 1846 was a turning point in the history of anaesthesia. when *Morton* made clinical trial of Ether. It was soon followed by introduction of other inhalational agents by our ancestors.

In 1934, an amiable modern leader in the speciality of anaesthesia, *J.S. Lundy* introduced intravenous technique of thiopentone administration and coined the term "Balanced Anaesthesia".

As the modern anaesthesia began around 1940, the first change was the initial use of curare product during Anaesthesia by *Griffith & Johnson of Montreal* in 1942.. The muscle paralysing effects of this alkaloid, derived from a South American plant, had been known for centuries, and the site of action at the neuromuscular junction was graphically demonstrated by *Claude Bernard*. The first published account of the arrow poison. used by South American Indians, appeared with in 25 years of the discovery of new world.In the United States, crude extracts was employed clinically to treat spasticity and

to modify the convulsions induced during psychotherapy of depression and other psychoses.

Initially, when given the extract for experimental trial, *S.C. Cullen* of Iowa city and *E.M. Papper* of New York, independentaly, had deemed the paralytic effects to be too much a trespass to be introduced to the anaesthetic regimen. As, by that time, the value of supported or controlled ventilation was not adequately understood, nor were the effects of residual neuro muscular blockade in the recovery room at all appreciated. The importance of antagonism of residual blockade was unknown and the need for careful monitoring had not yet established, hence the general use of curare led to widespread repurcussions. Also following the admonition of W.T. Salter, a pharmacologist of *Yale*, that, *"without vision and research, the professions die"* research in anaesthesia began.

In 1947, *Bovet* described Gallamine Triethiodide, which was first used clinically by *Huguenard* and *Boue* in 1948 in France and by *Mushin* (1949) in Britain. Gallamine was synthesized by pharmacologists to meet the demands of synthetic agents, that could be produced in a large bulk as an alternative to and with similar actions of tubocurarine.

In 1949, *Organe, Paton and Zaimis* introduced Decamethonium but latter most anaesthetists found that its disadvantages viz. development of phase II block and its excretion exclusively by the kindeys, outweighed its attractive features of rapid onset of action and profound relaxation.

In 1951, introduction of Succinyl Choline by *Thesleff & Foldes et al.* revolutionized anaesthetic practice. The main advantage of this drug was its early onset and brevity of action, for which this agent is in common use even today.

Other agents introduced into the clinical anaesthesia included - Fazadinium by *Hugin* and *Kissling* in 196,1 Alcuronium-a semisynthetic derivative of Strichnos Toxifera in 1964, and Pancuronium, first reported by *Baird* and *Reid* in 1967.

In 1979, a monoquaternary analogue of pancuronium, a newer agent, vecuronium was synthesized by *Savage*. Its main advantages are short duration of action, lack of cumulation and minimal cardiovascular side-effects in doses upto 20 times that required for paralysis. Simultaneously, in early 1980s, *Hughes & Payne and Chapple & Payne* described pharmacological profile of Atracurium Besylate.

Introduction of Vecuronium and Atracurium brought a revolutionary change in the anaesthetic practice because of their unique properties and with these two agents a new era of muscle relaxants has started.

PHYSIOLOGY OF NEURO - MUSCULAR TRANSMISSION :-

The scientific evaluation of neuro-muscular transmission began with Brodie's observation (1811) that when the lungs of curarized guinea pigs were inflated with oxygen, the dark colour of blood reaching the lungs was replaced by healthier blood of red colour. In the end of his simple experiment, he concluded that the action of curare was to suspend temporarily the function of brain.

It was nearly another 50 years before *Claude Bernard* carried out the experiments which proved conclusively that the action of curare was peripheral and not central as Brodie had proposed. But Bernard's experiments had far greater implications : by demonstrating that the junction between the nerve endings and the muscle fibre had peculiar properties, he established neuromuscular transmission as a separate physiological entity.

Although Claude Bernard established the specific properties of neuromuscular junction, the precise mechanisms of transmission had not then been demonstrated and as late as 1934 *Sir Henry Dale* in arguing the case for chemical transmission of nervous effects, was able to say. "I think I am right in supposing that the prevalent conception of the excitation of a voluntary muscle fibre by a nervous impulse assumes that the wave of physicochemical disturbance, propagated along the nerve fiber as the nerve impulse passes directly to the muscle fiber and there excites contraction as it is further propagated".

The first suggestion that nervous impulses might be transmitted by the release of a specific chemical stimulant, was made by *T.R. Elliott* in 1904. In an attempt to explain the close relationship between the actions of adrenaline and those of sympathetic nerves, he proposed that the nerves might release adrenaline at their endings. This idea was taken up by *W.E. Dixon*, who further proposed that parasympathetic nerves could also produce their effects by the release of chemical transmitter.

In 1914, the chance discovery of Acetyl choline, as constituent of a sample of erogot and therefore as a product of nature, caused *Sir Henry Dale* to make a detailed study of its properties and led to the discovery of its muscarinic and nicotinic properties.

Until 1921, the electrical theory of propagation of excitation across the myoneural and synaptic junctions was predominant and as late as 1933 *Otto Loewi* expressed the view that chemical transmission was unlikely to apply to the nerve endings in striated muscle. In contrast, in the same year *Lord Adrian* worte, "It is by no means certain that the humoral transmission of the vagus effect differs in kind from the transmission of activity from motor nerve to striated muscle. An exciting substance liberated at the nerve endings but destroyed with in a few thousandth of a second would have

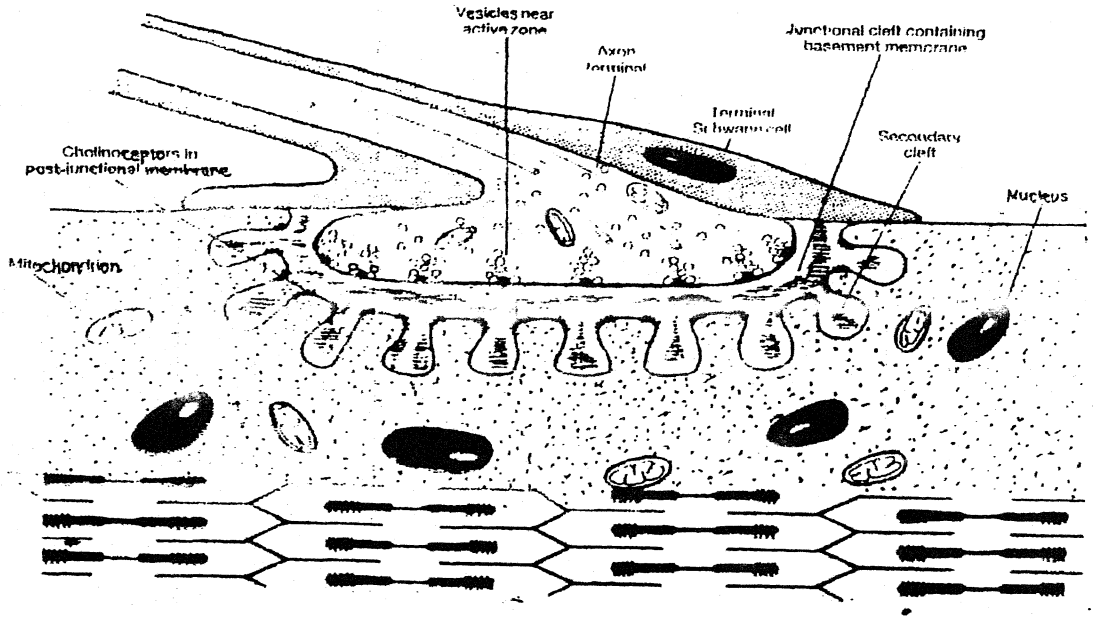


FIG. 1 NEURO-MUSCULAR JUNCTION

little chance of spreading by diffusion and would account well enough for the known properties of the nerve endings. It is equally likely that the more direct kinds of transmission depend on electric forces disturbing the balanced reactions of surface membranes.

As a result of the efforts of Dale and his colleagues and subsequent workers, the pattern of events in the chemical transmission in the nervous impulses across the neuromuscular junction has been reasonably defined.

Neuro-Muscular Junction : (Fig. 1.) :-

The motor nerve supply reaches to the muscle as a myelinated axon which divides into branches to supply 5 to 300 muscle fibres. As the nerve branch aproaches the muscle, it loses its myelin sheath and further subdivides to from fine terminations, about 100 microns long, which lie in grooves on the surface of the muscle.

The presynaptic membranes ensheath the nerve endings and is separated from the muscle membrane by a minute but distinct extracellular gap which in turn is partitioned by a basement membrane. In the vicinity of the nerve endings, the musle membrane becomes highly specialized to form the post-synaptic membrane, arranged in a series of regular folds, about one micron deep. These folds in which cholinesteraseis now known to be concentrated run into the muscle at right angles to the direction of the nerve endings.

Acetyl choline is synthesized in the nerve terminal by the action of the enzyme, choline transferase, on choline after its absorption from the surrounding extracellular fluid. Choline itself is derived from the hydrolysis of acetyl choline by cholinesterase.

When an impulse reaches the nerve termninal, some of the readily available acetylcholine is released. During repetitive nerve stimulation, the fraction of this read-

ily available pool released by an individual impulse is determined by the amount present at the time of stimulation, by the amount of previous activity and by the calcium ion concentration.

Interference with neuromuscular function will occur if the release of acetyl choline at the nerve endings is inhibited; if acetylcholine already released is prevented from occupying the receptors at the motor end-plate or if the excitability of the muscle membrane in the vicinity of the motor end plate is reduced.

ASSESSMENT OF NEUROMUSCULAR FUNCTION :

The first attempt at the quantitative assessment of neuromuscular function, in man, was made in 1932 by *Lanyard. West* who endeavoured to use curare for the relief of certain spastic states. To assess the value of his treatment, he devised a simple apparatus to measure the force, required to extend the leg at the knee joint in a seated patient before and after the injection of curare.

Despite the pioneering efforts of a few dedicated clinicians like West, neuromuscular function remained largely of academic interest, until, during world war II, *Griffiths & Johnson* (1942) were persuaded to use curare to reduce the tone of abdominal muscles during surgery.

The advent of neuro muscular blocking drugs saw the introduction of new techniques for their quantitative assessment and perhaps for the first time, a general need for precise measurement in clinical medicine.

Mushin and his Colleagues in 1949 used a dynometer to measure the power to flex fingers in volunteers before and after the intravenous injection of Gallamine. At the same time, they measured the contractile force of the rectus abdominis muscle by means

of a spring loaded pad applied directly over the anterior abdominal wall. Three years later *Bodman* (1952) compared two new curarizing compounds with tubocurarine by measuring the effect of drugs on the hand grips of conscious volunteers. In Bodman's method the strength of the hand grip was assessed by compressing a rubber bulb filled with water which was connected to a mercury manometer.

But such methods had the disadvantage, that the evidence for interference with neuromuscular transmission was made to correlate muscle weakness with nervous activity. In addition, these tests that depended on the voluntary control, could only be carried out on concious volunteers.

In 1955, *Mapleson and Mushin* described a method, which involved measuring the tension developed by the contractions of the small muscles of the thumb, when submaxinal tetanic stimuli were applied to the median nerve, at the wrist by means of surface 'Multi-wick' electrodes. *Poulsen and Houge* also stimulated the median nerve when they studied the effects of some curarizing substances on conscious voluteers.

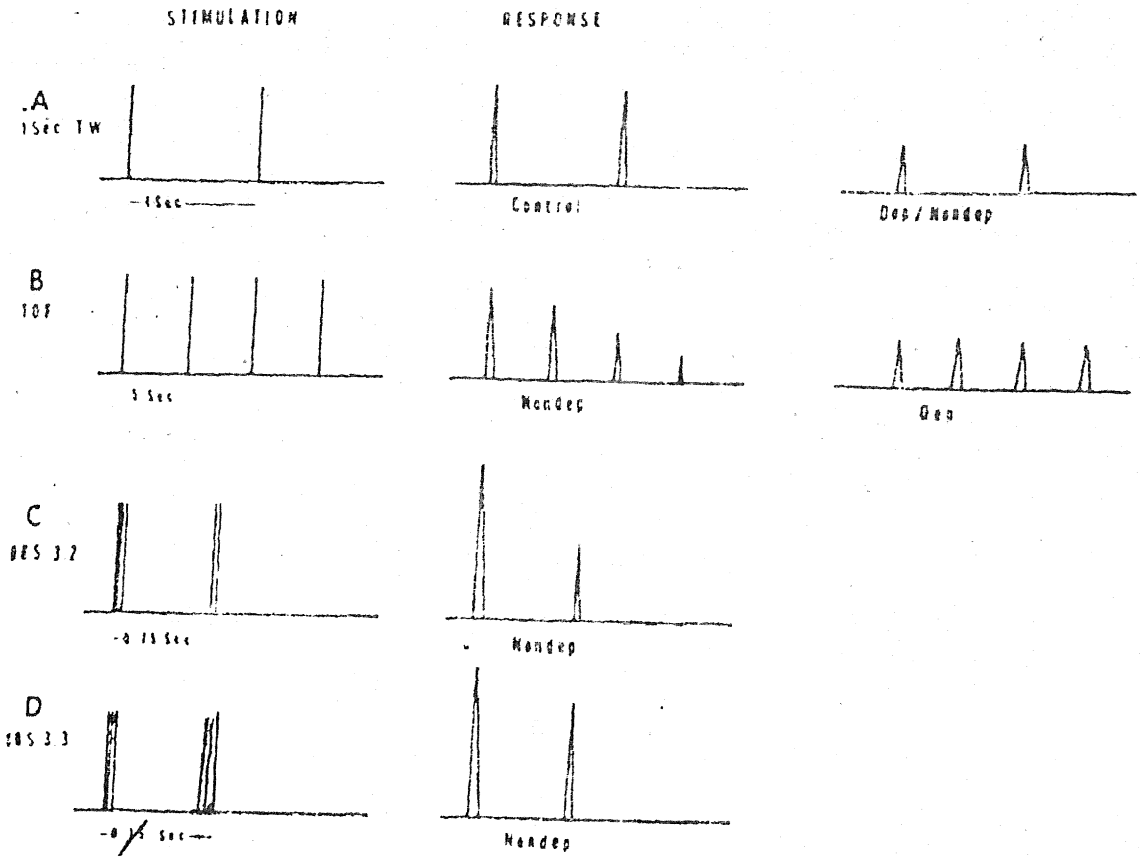
Another convenient method was that employed by *Payne* and *Holmdahl* (1959) to study the effects of repeated and continuous injections of suxamethonium. For this purpose a supra-maximal stimulus, provided by a square-wave pulse of 0.5 m/sec. duration, at 70-100 volts, was applied through a surface electrode placed over the ulnar nerve in the region of elbow - joint. The resultant twitches of the two medial fingers connected through a pivot, to a steel spring myograph, were recorded on a rotating drum. A more accurate method, measuring the contraction of adductor pollicis following supra-maximal stimulationof the ulnar nerve at elobow and wrist joint has been described by *Katz* (1965).

A more sophisticated and possibly more elegant technique for the analysis of neuromuscular transmission is that employed by *Desmedt* in 1957, in which electrical response of adductor pollicis muscle, while stimulated supra-maximally at elbow joint, was elicited with belly - tendon surface electrodes and recorded on a cathode ray oscilloscope, and photographed together with the isometric contractions recorded with a strain-gauge myograph.

The value of electro-myography in the assessment of neuromuscular blockade was realized by *Harvey* and *Masland* who described its use in 1941. The technique is based on the fact that when muscle fibres contract, action potential is set up and provided that the temperature and the intial muscle tension are maintained reasonably constant, a quantitative relationship exits between the voltage of the action potential and the number of fibres stimulated. Thus, such a voltage can measure the extent of neuromuscular activity. For recording, concentric needle electrodes are probably the most satisfactory but occasionally, if the patient is conscious, surface electrodes held in position with collodion are more suitable.

Although more convenient, spirometery offers a less satisfactory and less specific method of studying the action of neuromuscular blocking agents. A recording spirometer of the Benedict Rothtype is suitable and its value is enhanced if it is used in combination with recording pneumographs *(Mushin et al. 1949; Unna et al 1950).*

Spirometery presents no problem during anaesthesia if closed system of administration is employed, since the spirometer can be substituted for the reservoir bag of the anaesthetic circuit and records can be made directly. But if a Magill attachment with partial rebreathing is in use, then direct records are not possible without



Patterns of stimulation and response. A, Single stimulus stimulation at 1 Hz (1 stimulus/ sec). The height of the control twitches are noted. With either a depolarizing or a nondepolarizing block, twitch height is decreased B, train-of-four stimulation. Four successive single stimuli are delivered with 0.5-sec intervals. With a nondepolarizing block, there will be progressive depression of the response with each stimulus (fade). With a depolarizing block, the responses will be depressed equally. C and D, Double-burst stimulation. Three stimuli are delivered at 50 Hz, followed 0.75 sec later by two or three similar stimuli. There will be depression of the response to the second burst with a nondepolarizing block. There is increased height of the response to the first burst compared with that seen with train-of-four stimulation.

Fig. 2

conisiderable modifications of the appartus. Satisfactory tracings however can be obtained indirectly, if the reservoir bag of Magill attachment is inserted through the neck of sealed aspirating bottle which is connected by wide-bore tubing to the spirometer *(Brennan 1956).*

Ulnar nerve stimulation provides most convenient conditions because of its accessibility during most surgical procedures and because of anatomy of muscles involved. The ulnar nerve innervates the adductor pollicis, abductor digiti quinti, and the first dorsal interossequs muscles. The force of contraction of the adductior pollicis muscle is most commonly monitored. The response is easily seen, felt or quantified. Because this muscle is on the side of the arm opposite to the site of stimulation, there is little direct muscle stimulation, which could lead to underestimation of the neuromuscular blockade.

PATTERNS OF NERVE STIMULATION : (Fig. 2)

A century ago, *Wedensky* reported that the curarized muscle preparation shows an "apparent inhibition" in its response to indirect stimuli repeated rapidly. Based on this fact, various patterns of nerve stimulation are described.

These include :-

(1) SINGLE TWITCH : (Fig. 2-A)

Single twitch stimuli are usually delivered at a frequency of 0.1 or 1 Hz. It should not be applied more frequently than every 10 sec., as this is associated with a progressively diminished response and could result in over stimulation of neuromuscular blockade. *(Ali HH & Savcerese JJ).* The strength of a (control) response is noted and the strength of subsequent responses are then compared with the control and expressed as a percentage of control (single pulse or twitch depression , T_1%, T_1:T_c). With both a

non-depolarizing and a depolarizing block, there will be progressive depression of the response, as the block develops. A decrease in temperature will also cause a reduction in twitch response (Erikson LI, Jenson E, Viby Mogenson, 1988). Diasadvatages associated with its use include :-

(a) There needs to be a pre-relaxant control twitch.

(b) It can not distinguish between a depolarizing and non depolarizing block.

(c) The presence of full twitch height does not guarantee that full recovery has occured.

(2) TRAIN OF FOUR (TOF) :- (Fig. 2-B)

The train of four consists of consecutive single pulse delivered at a frequency of 2 Hz for 2 sec (4 stimuli at 0.5 sec. intervals). The TOF should not be repeated more frequently than every 10 to 12 sec. Some have recommended an interval of not less than 20 sec.

The train - of - four pattern seen with a depolarizing block differs from that of a non-depolarizing block in that there is equal depression of height with all four twitiches. With a non depolarizing block, there is progressive depression of twitch height with each twitch (fade). Thus counting the number of twitches (Train of four count or TOFC) permits quantitative assessment of a non depolarizing block. *(LEE CM 1975)*

Train of four ratio (TOFR or $T_4 : T_1$) is the ratio of magnitude of the fourth and first response. A progressive decrease is seen below a skin temperature of 32 degr :e C. Because TOFR requires that four twitches be present, it can not be used to monitor deep blockade. Testing at 10 mA above the lowest current, at which four responses can be

elicited, may provide values that are consistent with those of supra-maximal stimulus testing. *(Silverman DG, Conelley NR, O'Conner TZ 1991)*

Advantages of TOF include -

(a) More sensitive indicator of residual neuro-muscular block than single twitch.

(b) Establishment of control is not necessary.

(c) Can distinguish between depolarizing & non-depolarizing block and can detect development of phase II block.

Main disadvantage of train of four is that it is not possible to detect fade reliably using visual and tactile methods.

(3) DOUBLE - BURST STIMULATION - (DBS) : (Fig. 2 c, d)

It consists of two short tetanic stimuli separated by 750 m.sec. DBS 3, 3, consists of a burst of three 0.2 m. sec. impulses at 50 Hz, followed 750 m. sec. later by an identical burst.

DBS 3,2 is a burst of - three impulses followed by two such impulses 750 m. sec. later. It should not be repeated at intervals of less than 12 sec.

The primary use of DBS is to detect residual neuro-muscular blockade. It is more sensitive than TOF for identifying fade, using visual or tactile monitoring. It has also been used for intra-operative assessment of blockade. DBS causes more discomfort than train of four stimulation, but less than tetanic stimuli.

4. TETANIC STIMULATION

Tetanus is a rapidly repeated stimulus. In the absence of blockade, this causes sustained contraction of stimulated muscles. With a depolarizing block, tetanus will be depressed in amplitude but sustained. With a non-depolarizing block, tetanus is depressed in amplitude and there is a fade or decrement. It may be better to use 100 Hz than 50 Hz when assessing residual blockade but frequency used most commonly is 50 Hz, because it stresses the neuromuscular junction to the same extent, as a maximal voluntary effort.

The duration of the tetanic stimulus is important, because it affects fade. A duration of 5 sec. is standard. With a non-depolarizing block, fade is normally seen after only 1 or 2 seconds.

POST TETANIC FACILITATION (PTF) refers to a transient augmentation of response to stimulation that follows a tetanic stimulus. It is seen with non depolarizing blockers and is greater with deeper blockade. PTF is maximal in about 3 sec. and lasts upto 2 min. following a tetanic stimulation of 50 Hz applied for 5 sec. It should not be repeated more often than every 2 min. as this could lead to under - estimation of block-ade.

Post tetanic count is performed by administering single stimuli at one Hz followed by a tetanic stimuli of 50 Hz for 5 sec. After a 3 sec. pause, the single twich stimuli at 1 Hz is repeated and the number of posttetanic responses are counted.

A significant disadvantage of tetanic stimulation is that it is very painful. Therefore it should be avoided in unanaesthetized patients.

PHARMACOKINETICS OF MUSCLE RELAXANTS

DOSE-RESPONSE RELATIONSHIPS :-

Dose-response relationships can be used to indicate drug efficacy or potency, enhancement of drug action, or antagonism. The typical dose-response curve is linear in the range between 20% and 80% : linearity between 1% and 99% can be achieved by using a probit transform of the percent paralysis. After log-probit transformation, the data are correlated by linear regression analysis and the confidence intervals obtained.

INITIAL DOSE :- Dose - response curves for the NMBAs are best obtained from administering a single bolus of the relaxant and recording the peak intensity of effect. Comparative studies may require many subjects, when several drugs are evaluated. Fewer subjects are necessary when dosage is cumulative, i.e. when several dose increments are administered to a single subject *(Donlon JV, Ali HH, 1973)*. The single - dose and cumulative techniques yield comparable results for pancuronium and tubocurarine but not for atracurium or vecuronium, due to partial recovery between doses with the shorter - acting agents *(Gibson FA., Mirakhur R. 1984)*. Many drugs interact with the NMBAs, most to potentiate the intensity of blockade, such as the shift to the left of the dose response curves produced by the inhalational anaesthetics. In would appear, that this is more marked with the longacting NMBAs than with atracurium or vecurouium *(Miller RD, Rupp SM, Sohn YJ 1984)*.

INFUSION DOSAGE : Dose requirements for continuous surgical relaxation also can be determined when the desired intensity of paralysis is maintained by a stable rate of administration. The relative potencies of two NMBAs obtained by this method may differ from that with the single bolus dose.

Several groups have studied the dose of NMBAs given by continuous infusion, usually to maintain 90% depresion of the twitch response initially obtained after a bolus dose.

Predetermined blockade		Dose kg/min.	n
ATRACURIUM	50	4.0	10
	90	6.4	10
	90	6.1	10
	95	6.1	12
	90-99	7.2	12
VECURONIUM	50	1.0	10
	90	0.91	09
	90	1.2	08
	95	1.0	15

(Infusion dose-response relationship where the dose is varied to maintain at a predetermined level)

Many factors may affect the infusion rate required to maintain an intended magnitude of twitch depression.

CONCENTRATION - RESPONSE RELATIONSHIPS :-

When equilibrium occurs in the body, there is a constant relationship between concentrations in the plasma and at the neuromuscular junctions, and the sensitivity of an individual can be described in terms of this steady state plasma concentration (Css).

EFFECTS OF INHALATIONAL AGENTS :-

The potent inhalational agents produce a dose dependent shift in the concentration-response relationships for tubocurarine. During anaesthesia with enflurane, sensitivity to blockade increases in the second and third hours. *(Stanski DR, Ham J, Sheiner LB 1980)*

THE EFFECTS OF AGE :-

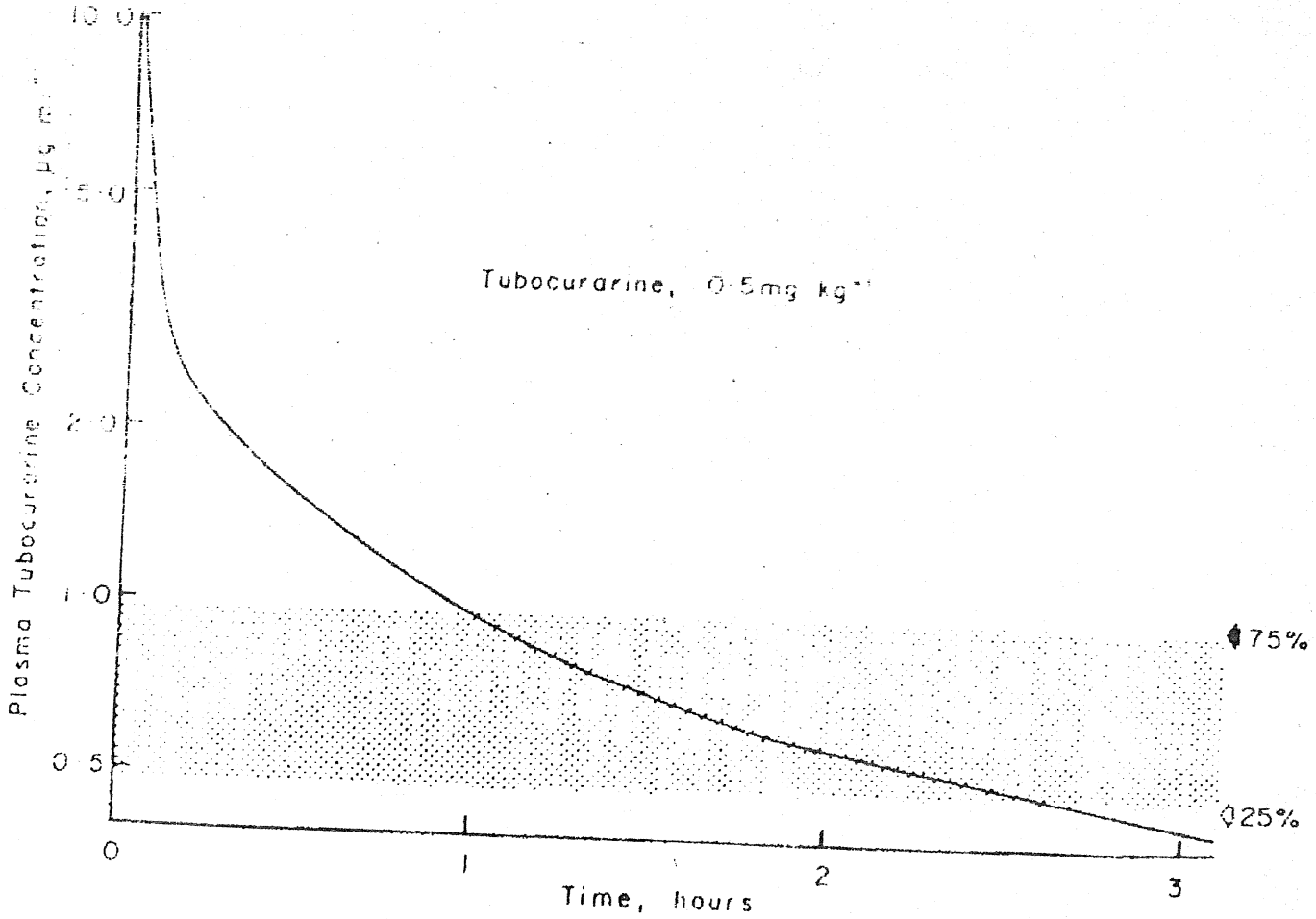
Both neonates and infants have a lower Css_{50} for tubocurarine than do children and adults *(Fisher DM, O' Keefe 1982)*. The effects of this on the dosage requirement for tubocurarine is offset by the neonate's larger steady state volume; similar differences between infants and children are seen with vecuronium *(Fisher DM, Castagnoli K, 1985)* There is no change with increasing age in the plasma concentration-response curves when elderly patients are studied with the use of pancuronium, vecuronium, metocurine, or tubocurarine *(Rupp SM, Fisher DM 1983)*. This suggests that the reduction in the infused dose of vecuronium, but not atracurium, required by elderly patients should have a pharmacokinetic explanantion, i.e. reduced clearance. *(d'Hollander AA, Luyckx C, Barvais L, De Ville A., 1983)*

THE EFFECTS OF RENAL AND HEPATIC DISEASES :-

Sensitivity to the NMBAs appears to be unaffected by renal failure, cirrhosis, or biliary obstruction. These diseases are not associated with change in the concentration - response relationship of Atracurium *(Wards, Neill EAM 1983)*, Gallamine, Pancuronium, Tubocurarine, or Vecuronium *(Lebrault C, Berger LJ, Denzel D 19085)*. Relative resistance to metocurine is reported in the presence of chronic renal failure.

EFFECTS OF HYPOTHERMIA :

In humans, sensitivity to tubocurarine is either not different or lessened. Hypothermic cardiopulmonary bypass reduces the dose requirements for pancuronium, atracurium, alcuronium, vecuronium and tubovurarine *(Flynn PJ, Hughes R, Walton B, Jothligham S, 1985)*



The early plasma concentration-time curve for tubocurarine, 0.5 mg. kg^{-1} based on a triexponential equation.[77] A longer chart duration would show the continuation of the plasma concentrations as a straight line after the second hour, the elimination phase; the linearity of this phase results from plotting plasma concentrations on a logarithmic scale. The shaded area indicates the range of plasma concentrations associated with 25-75% neuromuscular blockade.

Fig. 3

PHARMACOKINETICS OF SINGLE BOLUS DOSE :-

In most studies, pharmacokinetic estimates for each individual are derived from the plasma concentration time data obtained following a single bolus dose. Derivation of the volumes of distribution, half lives, and clearance assumes that these values remain constant throughout the study and also implies that these values are independent of drug dosage or the technique of administration. When plasma concentration are plotted on a logarithmic state (Fig. 3) this curve is seen to be multiexponential. This usually is characterized as biexponential or triexponential equation.

The triexponential equation describing the plasma concentration (Cp) at any time (t) is -

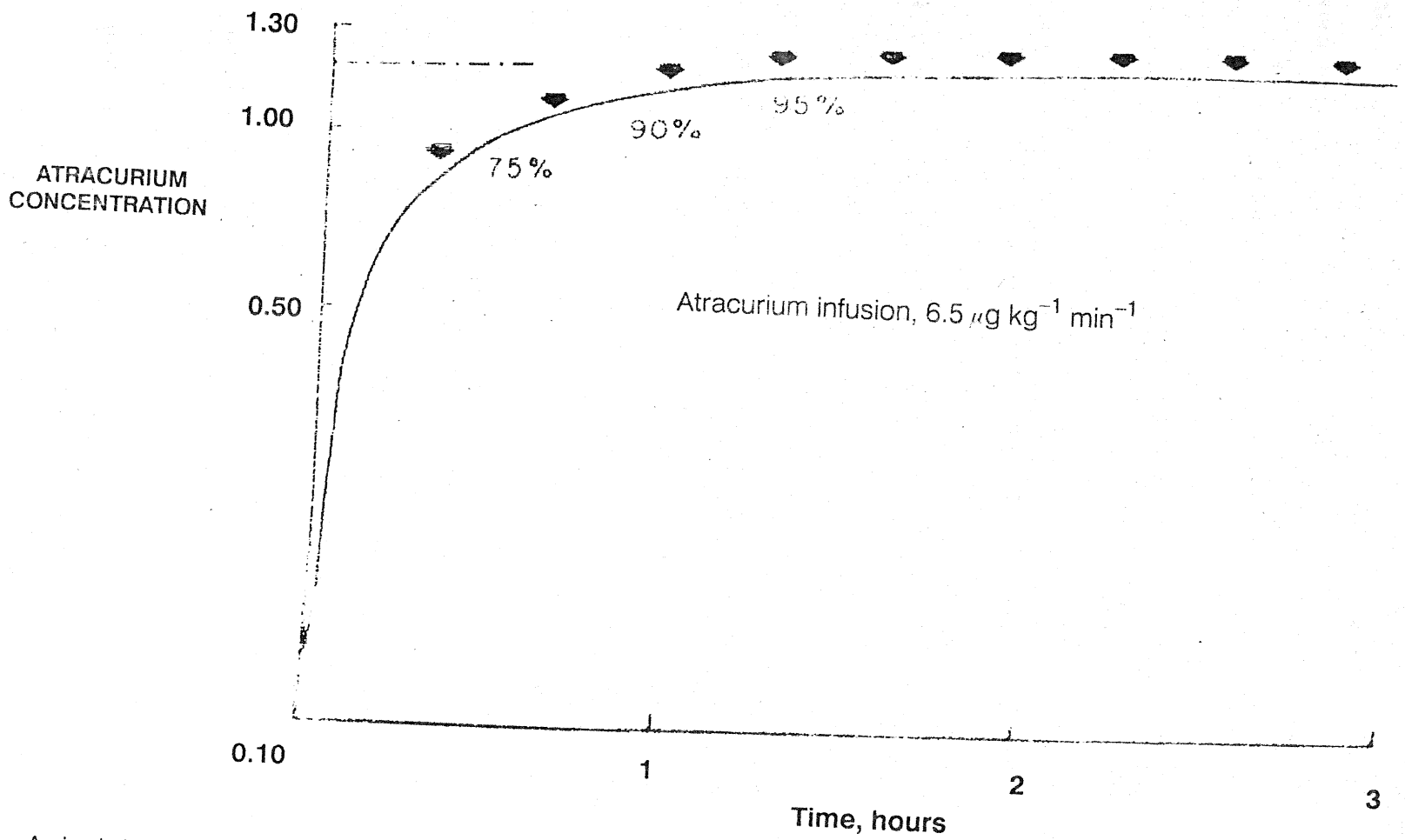
$$Cp^{(t)} = P_e^{-\pi t} + A_e^{-\alpha t} + B_e^{-\beta t}$$

The coefficients P, A and B include the dose as a factor and can be scaled. The terminal part of the concentration time curve has a negative slope (β) which is proportional to the clearance and is inversely proportional to the elimination half-life. As this part of the curve has the least slope, decreases of plasma concentration through a specific range (fig. 3) takes the maximum amount of time, when it occurs during the elimination phase. A further increase in dose will increase the time interval before the upper limit of concentration range is achieved, but not the time taken to traverse the range.

PHARMACOKINETICS OF A DRUG INFUSION :

The pharmacokinetics of a fixed-rate infusion predictate an eventual steady state plasma concentration (Css) according to the following equation:

Css = infusion rate / clearance.



A simulation of atracurium infused at a fixed rate to achieve a steady state of 1.3 μg - ml^{-1}. As with any infusion, it takes almost three half-lives (arrowed) to reach 90% of the steady state concentration and more than four half-lives to reach 95%. A more rapid infusion would have the same time sequence but achieve a greater steady state concentration.

Fig. 4

This plasma concentration is analogous to the water level maintained in a barrel when the flow entering is equal to the rate at which water leaks out through a hole in its base. The rate at which Css is attained depends on the half-lives of the drug : for the relaxants the distribution half life is short enough to be neglected and the rate of attainment of steady state during continuous infusion then depends only on the elimination half-life. The fraction of the steady state level achieved can be described in terms of multiples of the elimination half-life. (Fig. 4)

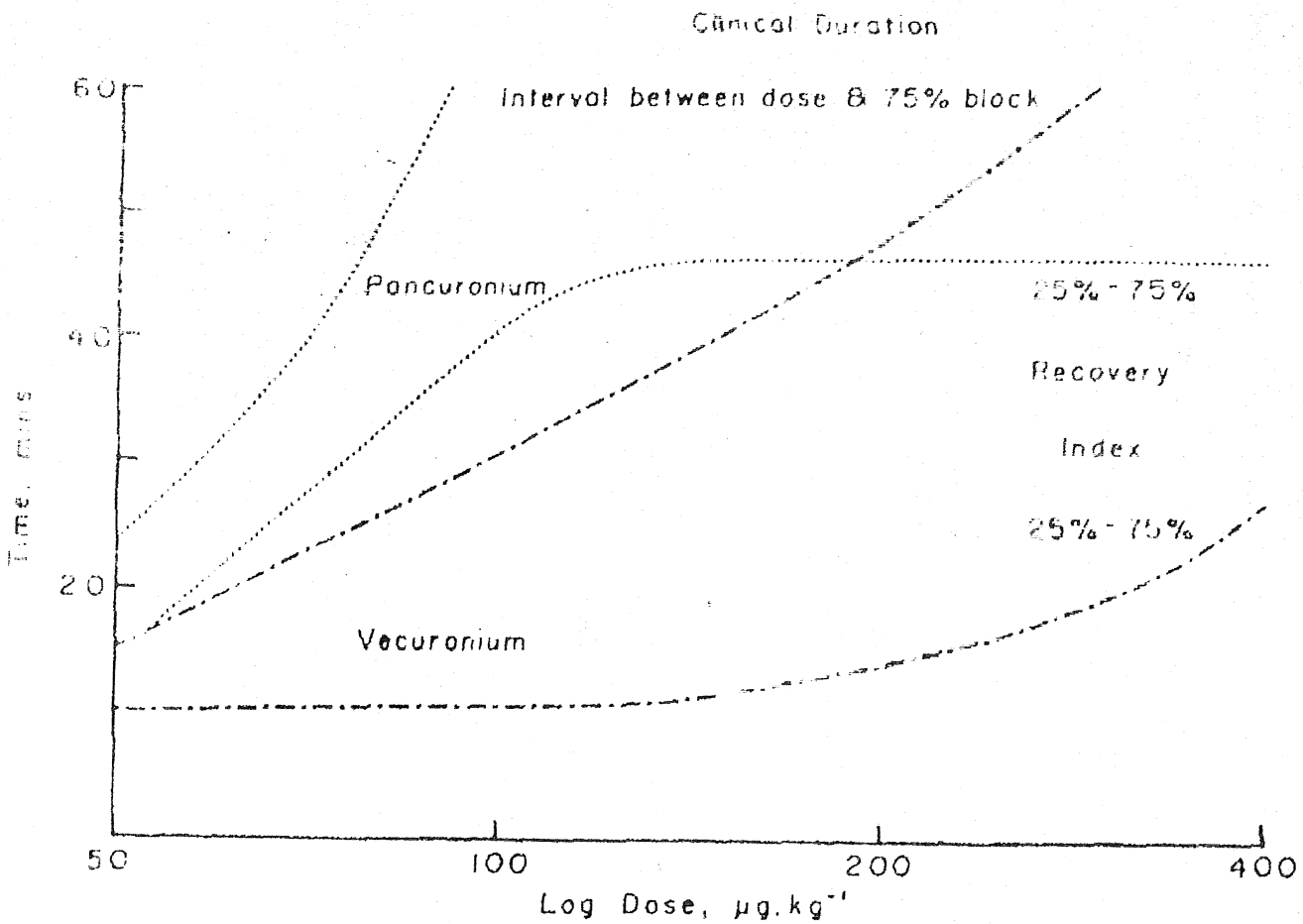
PLASMA PROTEIN BINDING

All of the assay techniques for the NMBAs measure the total concentration of the compound in the plasma, but it is the unbound drug that influences events at the neuromuscular junction. When the proportion of drug bound to plasma proteins exceeds 90%, then variablity in the extent of binding can have an important effect.

Most protein binding studies have been performed with tubocurarine, the relaxant demonstrating the highest percentage of protein binding. Its binding does not differ from the normal in patients with liver disease, renal disease, or cardiac disease. While a systematic investigation of the effect of relaxant protein binding on kinetics or dynamics has not been performed, these data suggest that variations in 0-50% plasma protein binding are of minimal importance in explaining variations in response to the NMBAs.

PREDICTING THE TIME COURSE OF SPONTANEOUS RECOVERY :

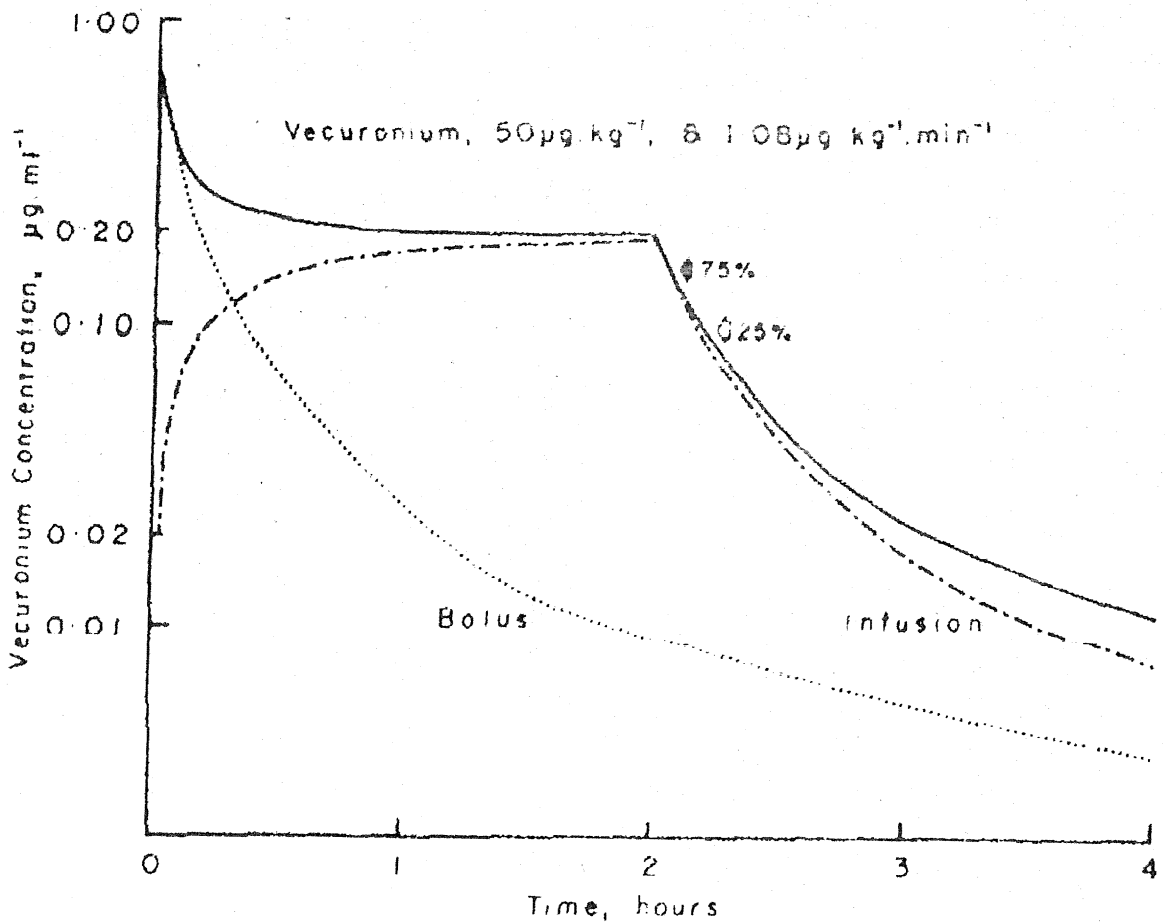
Although spontaneous recovery from 75% paralysis to 25% paralysis appears linear, it was precipitated from early tubocurarine data that there should be a dose dependent rate of decline of its pharmacologic effects. plasma concentrations associated with 25% depression of twitch height are approximately twothirds those for 75%



Predictions of the time course of neuromuscular blockade with single doses of pancuronium (dotted line) and vecuronium (dot-dash). The upper lines for each relaxant represent the interval between its administration and spontaneous recovery to 75% twitch depression. The lower lines show the dose-dependent change in the 25-75% recovery time; for pancuronium this plateaus with doses in excess of 0.15 mg . kg^{-1}.

Fig. 5

depression. A specific range of concentrations suggests that the recovery index is influenced chiefly by the shape of the plasma concentration time curve between the upper and lower limits of the range. When plasma concentration - time curves were constructed, the times at which specific plasma concentrations would be present after a single dose of relaxant could be predicted. Increased dosage transposes the curves upward, and concentrations remain longer in the range, producing surgical relaxation above concentrations associated with 75% twitch depression. This duration of clinically useful blockade increase with greater doses, and (Fig. 5) predicts that this effect will be more marked with pancuronium than with vecuronium; it also predicts that the recovery index (minutes between 75% and 25% blockade) will plateau with doses of pancuronium in excess of 0.15 mg.kg^{-1}, Similar plateau occurs with atracurium at doses of 0.3 mg kg^{-1} or more. With doses of atracurium in excess of 0.2 mg-1 kg-1, there is a linear relationship between the logarithm of the dose and the time interval between injection and spontaneous recovery to a particular intensity of blockade. *(Bevan DR 1985).* The "Pharmacodynamic half-life" of atracurium derived from the slope of these regression lines (e.g. , for 75% twitch depression) averages 16.5 min. The short distributive phase and clinically useful elimination phase of atracurium is in marked contrast to the redistribution seen in the vecuronium bolus curve during its first two hours. Fig. 6 suggests that it would require more than a tenfold increase in the bolus dose of vecuronium before the elimination phase would be superimposed on the range of concentrations depicted by the arrows. Equipotent doses of atracurium appear to derive their similar durations of action completely different pharmacokinetic base : recovery from atracurium - induced blockade is almost entirely related to its clearance, while that from vecuronium depends largely on its redistribution.



A combined bolus and infusion of vecuronium calculated to attain a steady state concentration of 0.2 μg . ml^{-1}. The solid line represents the plasma concentrations obtained as the sum of the bolus (dotted) and the 2-h infusion (dashed) values. As two half-lives equal 3 h, the infusion curve is still rising at 2 h, and blockade then would gradually increase to 95% as the infusion attains steady state. The plasma concentrations related to the bolus alone and following cessation of the infusion indicate the major role of redistribution in spontaneous recovery from vecuronium-induced blockade.

Fig. 6

COMBINED BOLUS AND INFUSION REGIMENS

The theoretic basis for rapidly achieving constant concentations of a durg in plasma is provided by *Mitenko* and *Ogilvie* (1972). Their calculations for a combined bolus and infusion are based on a two-compartement open system model. They point out that the concentration in plasma at any moment can be thought of as the sum of the bolus curve and the infusion curve. It then becomes possible to calculate a regimen that matches the elimination phase of the bolus against the rising concentration curve of the infusion to achieve the earliest possible plateau (Fig. 6).

In group of studies a predetermined infusion of relaxant has been adminstered at a fixed rate, commencing simultaneously with the initial bolus dose. When this dosage regimen is appropriate to the patient, the bolus dose produces 90 to 99% twitch depression, which then is maintained for the duration of the infusion. After the first hour of the infusion, this continuous effect is associated with a plateau in the plasma concentrations of relaxant.

While studies with a fixed infusion rate have the disadvantage that they do not accomodate the nonaverage patient, they do indicate a regimen that may need only minimal modification to be suitable for many patients.

PHARMACODYNAMICS OF NONDEPOLARIZING MUSCLE RELAXANTS

Available nondepolarizing muscle relaxants include a variety of agents that can be classified according to chemical class i.e. the steroidal compounds or benzylisoquinolinium substances, or according to durationof action (long, intermediate or short actiong). All the nondepolarizing durgs block the neuromuscular junction by competitive inhibition of Acetylcholine at nicotinic receptors. Various pharmacodynamic effects of these drugs include -

AUTONOMIC EFFECTS

(a) NICOTINIC AND MUSCARINIC EFFECTS -

Neuromuscular blocking drugs, interact with the acetyl choline at nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junctions.

Interaction with cholinergic receptors form the basis for most of the cardiovascular side-effects of muscle relaxants. The depolarizing agents potentially block all autonomic sites. However the likelyhood of autonomic blockade by these drugs, especially the newer agents, Atracurium Besylate and Vecuronium Bromide, is remote because the dose-response curves for autonomic inhibition lie far to the right of the curve for neuromuscular blockade.

(b) GANGLION STIMULATION -

The depolarizing relaxant succinyl choline may produce an elevantion in heart rate and arterial pressure secondary to the mechanism of ganglion stimulation, which is probably mediated by activation of nicotinic receptors on ganglion cells on both sides of autonomic nervous system *(Goat VA, Feldman SA 1972).*

(c) GANGLION BLOCKADE :-

Ganglion blocking effects of d-TC occur closer to the neuromuscular blocking effects than in the case of any other muscle relaxant. *(Harrision GA-1972) (Highes R, Chapple DJ-1976).* Nevertheless, the principal reason for the hypotensive property of dTC is its histamine releasing action. *(Moss J, Rosow FE, Savarese JJ et al. : 19(1).* Atracurium & Vecuronium have no effect on autonomic gangila.

(d) MUSCARINIC BLOCKADE :-

Vagal block resulting in tachcardia, is produced by muscarinic blockade at the sinus node of the heart in response to pancuronium and gallamine. Gallamine is potent vagolytic, where this side effect occurs within and overlaps the dose range for N M blockade. *(Marshall TG : 1982)*

The new steroidal relaxant rocuronium shows a dose ratio of vagal block to N-M blockade of about 0.3 Therefore Rocuronium may be slightly vagolytic at high dosage in human subjects. *(Melling Hoff H, Diefenbach C, Buzello W-1991).*

(e) HISTAMINE RELEASE :-

Quaternary ammonium compounds, such as muscle relaxants, are generally weak histamine releasing substances, relative to tertiary amines, such as morphine. Nevertheless, when large doses of certain muscle relaxants are injected rapidly by the intravenous route, some degree of erythema of the face, neck, and upper torso may develop, possibly together with a brief fall in arterial pressure and slight to modrate rise in heart rate. Bronchospasm is very rare. The side effect of histamine release is most often noted following administration of the benzylisoquinolinium class of muscle relaxants. The side effect may be reduced considerably by a slower injection rate. It is also prevented by prophylaxis with combinations of H1 and H2 blockers *(Hoskin et al. 1988)*. If a minor degree of histamine release occurs after an initial dose of muscle relaxant, subsequent doses will generally cause no response at all, as long as they do not exceed the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine.

An increase of histamine levels in plasma, to 200 to 300 percent of base line levels, causes a brief decrease in arterial blood pressure (1 to 5 minutes), an increase in

heart rate and skin erythema around the face and neck. The benzyl isoquinolinium substances d-TC, metocurine, mivacurium and atracurium release these amounts of histamine in a dose range of 0.5 to three times the ED 95 for each compound. Thus, the safety margin for this side effect is about three times geater for atracurium and mivacurum and two times greater for metocurials than for d-TC *(Basta SJ, Ali HH, Saverese JJ 1983; Scott RPF, Saverese JJ, 1985).*

Hosking et al. (1988) conducted a study performed with atracurium. They gave 1.5 mg/kg (six times the ED 95) Atracurium as an intravenous bolus. Not surprisingly, they observed a mean decrease in mean arterial blood pressure of 30% and a large (10 to 20 fold) increase in plasma histamine concentrations. Scott et. al. and Hosking et. al found that combined H1/H2 receptor blockade attenuated these histamine induced changes.

D.H. Lawson, G.M. Palace, R.J. Glanin, E.B. Andrews & H.Jick in 1989 conducted a study, in which they compared atracurium & vecuronium. They observed various features possibly related to histamine release such as hypotension, tachycardia, hypertension, bradycardia, arrhythmias and hypovalaemia. Major events (hypertension, bradycardia & dysrrhythmias were observed in 8 patients in Atracurium group (out of total 477 patients) and in 7 patients in vecuronium group (total patients, 484).

Hotono Y, Arai T, Nada J. et. al. (1990) showed that the hypotensive cardiovascular response to d-TC in man is prevented, not only by anti - histamines but also by non-steroidal antiinflammatory drugs.

The side effect of benzylisoquinolinium compound may be viewed as a pharmacological response, wherein, as dosage is increased, the percentage of individuals, responding with some menifestations of the side effect increases. This type of response

involves chemical displacement of contents of most cell granules containing histamine, prostaglandins and possibly other vasoactive substances. *(Basta SJ, 1992)*

CARDIOVASCULAR EFFECTS :-

The cardiovascular effects of neuromuscular blocking drugs are generally due to release of histamine, stimulation or inhibition of peripheral autonomic nervous system or increase in serum potassium level following motor end plate depolarization. This subject has been thoroughly renewed by Bowman, Domench, Gracia and Sasian (1982).

According to Crul & Booij (1980), no change in arterial pressure and heart rate occured after giving Org. NC 45 even in doses upto three times the ED 95 dose, where as some degree of tachycardia and an increase in arterial pressure were usually seen after giving pancuronium.

Vecuronium has been shown to be free from cardiovascular side effects *(Booij et al, 1980; Krieg, Crul and Booij, 1980).*

Atracurium has also been shown to be free from cardiovascular side effects *(Payne and Hughes, 1981)* and to cause histamine release only in doses, 8-16 times the neuromuscular blocking dose *(Hughes and Chapple, 1981).*

A comparative study of Org. NC 45 and pancuronium on heart rate and arterial pressure in anaesthetized man was done by Barnes et al (1982). They observed that bolus dose of Org. NC 45 caused no changes in heart rate. Animal studies have shown Org. NC 45 to be devoid of vagal blocking activity *(Booij et al 1980; Durant; Honwerttes and Crul, 1980).*

In a clinical study on Org. NC 45 by *Karr et al (1982)*, the heart rate and arterial systolic pressure changes for the first 30 minutes following injection of the intubating

dose. At 15 min. following injection and when the surgical stimulus was minimal or absent, there was no tachycardia *(Marshall et al 1980).*

Administration of Org NC 45 caused minimal changes in the heart rate and blood pressure during halothane or enflurane anaesthesia. On the other hand, some degree of hypotension & bradycardia was noted in patients anaesthetized with atracurium & halothane. In case of atracurium, hypotension could be because of histamine release *(Sergio et al - 1982).*

In a study by *Heskin MP, Lennon RL & Gronert GA (1988)* it was shown that Atracurium in doses greater than 0.4 mg/kg occasionally caused transient hypotension and it could be minimized by the slow administration of this muscle relaxant.

In several case reports *(Starr NJ, Sethna DH, Estfanous FG 1986),* severe brady cardia and even asystole are described, following vecuronium and Atracurium administration. All of these cases were associated with opioid administration. There can be many causes of badycardia during surgery. Subsequent studies indicate that vecuronium or atracurium alone do not cause bradycardia *(Cozantis DA, Erkola O. 1989), (Hull CJ 1989).* When combined with other drugs (e.g. Fentanyl) that do cause bradycardia, the nonvagolytic relaxants atracurium and vecuronium simply allow this mechanism to occur unopposed.

The effect of Atracurium, Vecuronium and Pancuronium on heart rate and arterial blood pressure in normal individuals were studied by *Lavery et al (1986).* Heart rate and rhythm (from ECG) and systolic, diastolic & mean atrerial pressure were measured for 30 min. following administrationof atracurium 0.5mg/kg., Vecuronium 0.08 mg/kg

or Pancuronium 0.1 mg/kg during steady state anaesthesia, with nitrous oxide, oxygen and either 0.75 % halothane or 4-5mg/kg Fentanyl. With halothane anaesthesia, atracurium causes only minimal changes in heart rate, systolic, mean & diastolic arterial pressures. The heart rate changes after vecuronium were minimal (a maximum fall of 7 BPM or about 9%). Changes were significant at 1 and 30 min. There was significant fall in systolic arterial pressure and mean arterial pressure (up to 15 & 19% respectively) during the period of 3-15 min. after administration of vecuronium. Diastolic arterial pressure showed a significant decrease throughout the 30 min. period after administration of pancuronium and fentanyl. Atracurium produced gradual reduction in heart rate, becoming significant at the 20,25 and 30 min. observation, when the decrease was of the order of 5-6%. Three to five min. after administration of atracurium systolic, diastolic and mean arterial pressure were decreased significantly ($p < 0.05$) but from that point arterial pressure began to increase and by 25-30 min., was significantly greater than control. Vecuronium showed no significant changes in heart rate. Arterial pressure showed significant decrease ($P<0.05$) 3-5 min. after vecuronium administration.

In an another study conducted by *Tullock WC, Diana P and Cook DR et al., (1990)* on cardiovascular stability of Vecuronium showed that, markedly reduced vagolytic property, together with absent ganglion blocking and histamine releasing effects, resulted in a noteworthy lack of cardiovascular responses throught a wide clinical dose range from one to eight times the ED 95 (0.05 to 0.40 mg/kg).

In a study, no clinically significant changes in heart rate or arterial pressure were observed with both Atracurium and Vecuronium. There was statistically significant decrease in heart rate after vecuronium, but this was small (4-5%), and was not considered clinically significant. Similar alterations in heart rate have been noted in other

investigations *(Barnes et al, 1982). W.M. Schramm, K.Strasser, K. Strasser, A. Bartunek and C.K. Spiss* evaluated the effects of single dose of rocuronium 0.6mg/kg. and vecuronium 0.1 mg/kg on ICP, MAP, cerebral perfusion pressure and heart rate in 20 neurosurgical patients. In the rocuronum gp. the change in intracramial pressure from base line varied from -3 to +4 mm Hg. and in the vecuronium gp. -4 to +2 mmHg. There were no significant changes in ICP, MAP & CPP in each group, even though MAP decreased slightly in rocuronium group. HR did not change in vecuronium group and significantly increased in rocuronium gp.

Deepak Tampe, S. Sinha (1995) conducted a study on 20 patients undergoing electrive valve surgery. They compared pancuronium and Atracurium and concluded that HR, MAP, mean pulmonary arterial pressure, & pulmonary capillary wedge pressure increased in pancuronium group and remained high at 5 min. after intubation except MPAP, mean arterial pressure & right ventricular stroke vol. returned to normal. In atracurium group/Cardiac index decreased from 3.05 ± 0.9 to 2.63 ± 0.7 L/min./m^2, mean arterial pressure, MPAP, pulmonary capillary wedge pressure & HR increased significantly at 2 min. after intubation but returned to control value at 5 min. after intubation.

V.Slavov, M.Khalil, J.C. Marie (1994) evaluated 80 patients, undergoing routine abdominal surgery, 40 patients were aged 18-50 years and 40 were more than 65 years. They found that duration of action of initial doses and repeat doses was similar in control group and elderly group. However, the initial dose of vecuronium caused a significant longer period of block in elderly patients and duration of repeat doses was also longer in this group.

P.B. Loan, P Elliotti, R.K. Mirakhur (1994) measured haemodynamic effects of atracurium and mivacurium in patients undergoing coronary artery by-pass surgery under fentanyl anaesthesia. There were no significant haemodynamic changes in the atracurium group other than transient decrease in pulmonary capillary wedge pressure. Mivacurium (0.15 mg/kg) produced 12% decrease in mean arterial pressure and 16% decrease in systemic vascular resistance index.

M. Naguib, A.H. Samarkandi, A.K. El-Bakrey (1995) examined the effects of different benzylisoquinolinium and steroidal neuromuscular blocking agents on plasma concentration of histamine, heart rate, and arterial pressure after single rapid injection of 0.2 mg/kg Mivacurium, 0.6 mg/kg Atracurium, 0.5 mg./kg Tubocuraring, 0.1 mg/kg vecuronium and 0.6 mg/kg Rocuronium. Mivacurium, Atracurium and tubocurarine caused 370%, 234% & 252% increases in plasma histamine concentration at 1 min. interval and 223%, 148% & 157% increases at 3 min. interval respectively. In contrast, rocuronium and vecuronium group had no significant changes in either plasma histamine concentration or haemodynamic variables. In Mivacurium, Atracurium and Tubocurarine group, increases in plasma histamine concentration corresponeded with decrease in mean arterial pressure and increase in heart rate with peak changes at 8 min. interval.

NEURO-MUSCULAR BLOCKADE

Atracurium and vecuronium are two new potent, short acting non-depolarizing neuromuscular blocking drugs. Vecuronium, the monoquaternary homologue of pancuronium, has been found to be five times more potent than Atracurium which is a bisquaternary tetrahydropapaverum derivative and results in comparable intubating conditions. *(Gramsted and Lilleaasen; 1982)*

In a clinical comparison of Atracurium and Org NC 45, by E.N. Robertson, L.H.D.J. Booij, R.J. Fragen and J.F. Crul (1983), pharmacodynamics of both drugs were comparable to previously reported studies. Vecuronium was significantly shorter acting than Atracurium. In some cases prolongation of recovery rate of vecuronium were noted which has also been noted in other studies, *(Agoston et. al. 1980)* but were not considered to be clinically significant. When greater doses of vecuronium were used, the increase in duration of recovery led to prolongation of the total duration of action. In contrast, the steady recovery rate of atracurium suggested that the metabolic pathways thought to terminate its effects (Hofmann elimination and ester hydrolysis) were not saturated at the doses used in this study.

In an another study by *Bowman W.C. (1983),* Vecuronium when given in doses equal to ED 90 (i.e. 43 µg/kg), onset time was found to be 5.0 ± 0.3 min. Duration $_{25}$- 10.9 ± 0.8 min & recovery rate 6.8±0.6 min. For Atracurium (188 µg/kg) these values were 6.7 ± 0.4 min, 17.1 ± 1.4 min. and 12.0 ± 0.5 min respectively. When both these drugs were used in doses 3xED 90, recovery rate for vecuronium was 13.8 ± 1.9 min while for atracurium it was 11.0 ± 0.7 min.

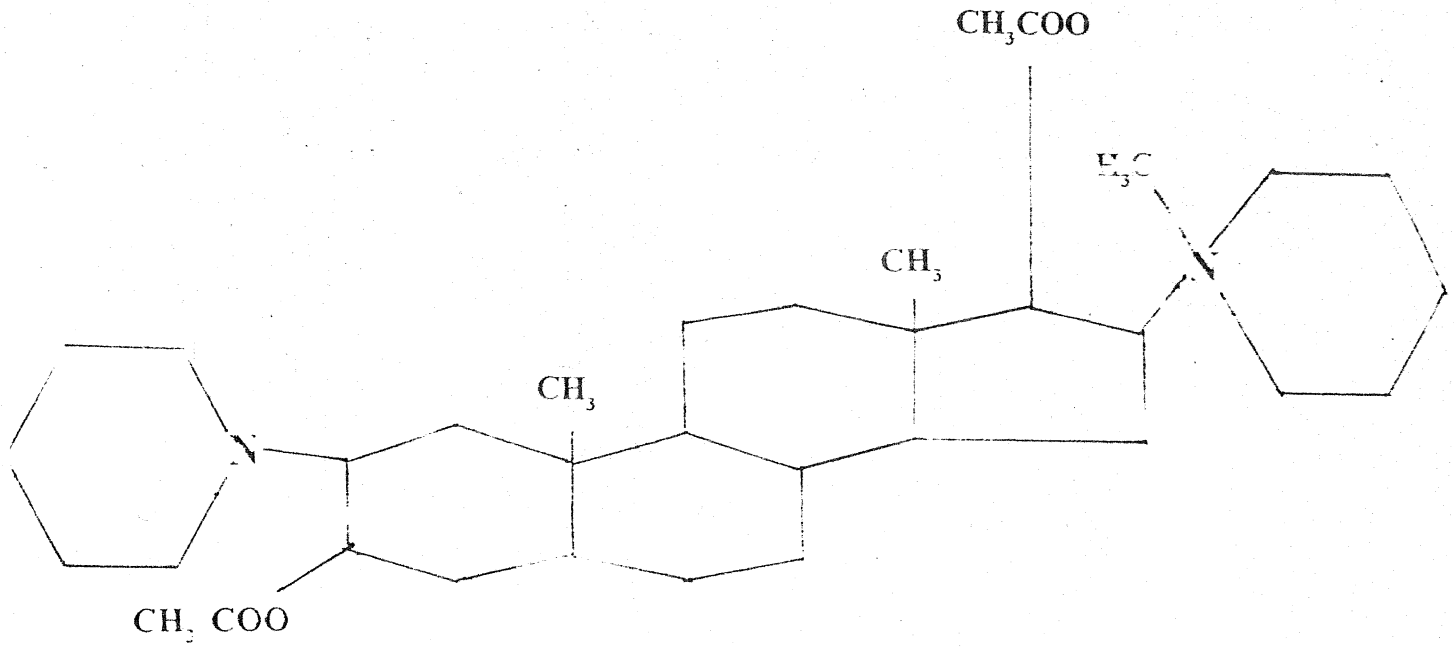
Margaret A.Gargarian, Salvatore J.Basta and Hasan H. Ali (1984) evaluated the efficacy of atracurium infusion and concluded that excellent muscle relaxation was achieved at a mean infusion rate of 8.4 µg/kg/min. . Recovery rate did not differ in between continuous infusion and bolus administration and length of atracurium infusion did not influence recovery times.

R.K. Mirakhur, C.J. Ferres and J.K. Pandit used vecuronium infusion at the rate of 0.083 mg/kg/hr and reported that time to 10% recovery of twitch height, follow-

ing initial bolus dose, averaged 26 min. The time taken for stabilisation of block after commencing vecuronium infusion was 15.4 min ± 6.5 min and time required for the twitch height to recover from 10% to 25% of control, on stopping the infusion averaged 7.4 min (Range - 4-12min)

G.Noeldge, H.Hinsken and W.Buzello (1984) compared continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium. According to their study, within 1.5 to 6 min. of the loading dose of either drug, total neuro-muscular blockade had been achieved in all patients. The duration of action of the loading dose of pancuronium to 25% recovery of twitch height, was 1 hr. being on an average 2.6 times longer than that for vecuronium. Repititive duration $_{25}$ was 42 ± 16 min for pancuronium and 12 ± 4 min for vecuronium. Time for spontaneous recovery from the end of infusion of vecuronium to 25% recovery was 20 ± 5 min and to 75% recovery was 42 ± 10 min.. Shortest recovery times were seen with repeated doses of vecuronium as compared to vecuronium infusion or intermittent bolus pancuronium which was 1.7 and 2.9 times longer respectively. The infusion of atracurium had been studied by *d' Hollander et at. in 1983.* Results were similar to findings of vecuronium used in the above study except for the recovery time which was 7 min shorter with atracurium than with vecuromium.

K.L.Gordon and C.S. Reilly (1989) conducted a study on recovery of neuromus cular function after infusion or intermittent bolus doses of Atracurium and vecuronium.. Assessment of recovery was done by grip strength and respiratory function testing. In the atracurium infusion group, mean time from the end of infusion to neostigmine administration was 10.8 min and in vecuronium group it was 11.3 min. There were more dose variations within the bolus dose groups than within the infusion group. Grip strength



CHEMICAL FORMULA OF VECURONIUM

Fig. - (7)

at 15 min. after antagonism of blockade was significantly less in vecuronium infusion group as compared to atracurium intermittent and infusion groups. In the atracurium group peak expiratory flow was greater than 90% of control by 60 min. (bolus dose) and 45 min. (infusion group). In the vecuronium groups, PEF had not achieved 90% by 90 min.

PHARMACOLOGY OF VECURONIUM & ATRACURIUM

VECURONIUM

Chemical Formula of Vecuronium (Fig. 7)

Vecuronium, 2-desmethyl analogue of pancuronium was recognized in mid -1970s, by *Savage, Durant, Bowman* and *Marshall*, as having much less vagolytic effect and a shorter duration of action than pancuronium in the cat. These pharmacological properties were subsequently confirmed in surgical patients. *(Agoston S, Salt P, Newton D et al.1980)* .

Cardiovascular side effects

Vecuronium is about 20 times weaker as a vagolytic substance than pancuronium. The structural feature responsible for this difference is the absence of 2- methyl quaternary group. This markedly reduces the acetyl choline like character of the A-ring substitution, resulting in less attraction to cardiac muscarinic receptors. The markedly reduced vagolytic property, together with absent ganglionic blockade and histamine releasing effects, results in noteworthy lack of cardiovascular responses throughout a wide clinical dose range, from one to eight times the ED

METABOLISM OF VECURONIUM IN LIVER

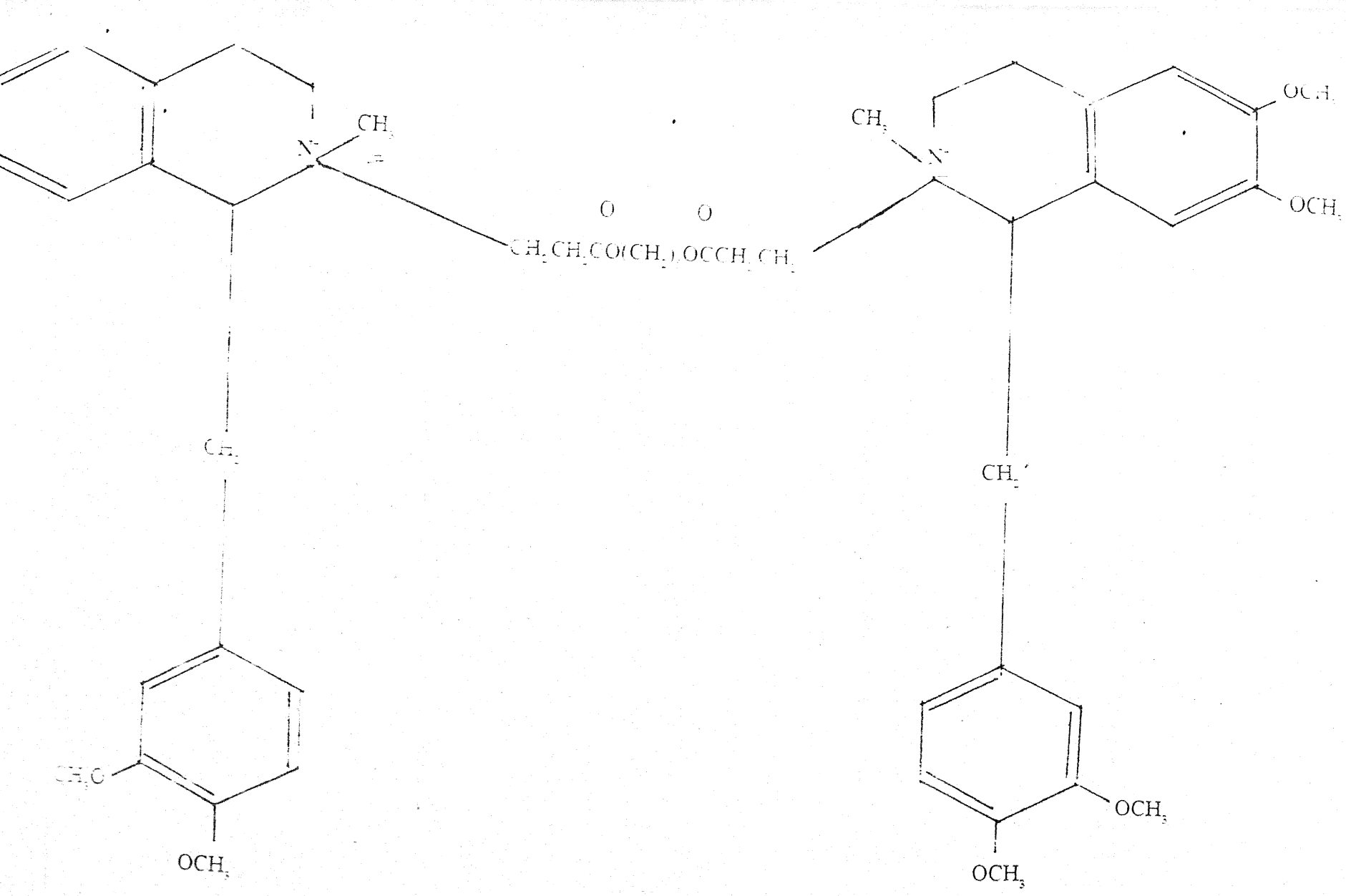
95 i.e.0.05 to 0.40 mg/kg *(Tullock WC , Diana P, Cook DR et al 1990)*

Metabolism and Elimination

Metablic pathways of vecuronium are shown in the fig.8. Vecuronium is deacetylated at the 3-position by liver microsomes. About two to three times as much is metabolized as pancuronium, such that 30 to 40 percent of vecuronium is eventually excreted as the 3.OH metabolites. Consequently, vecuronium has two major routes of elimination liver and kidney which are of approximately equal importance. The elimination of 3-OH metabolite in humans is not well defined. There is a possibility of its accumulation in renal failure during long term administration in I.C.U. . The excertion of vecuronium is diminished in the elderly and in young children, less than 1 year of age *(Bancini AF, Scaf AEJ, Sohn YJ et al 1986)*. The duration of action of vecuronium is longer in these groups of patients and recovery is slower than in young healthy individuals *(Lien CA, Matteo RS, Ornstein E. et al 1991)*. Vecuronium is nevertheless a good choice in severe renal dysfunction.

Doses of vecuronium.

	Dosage (mg/kg.)	Clinical Duration (min)
E D 95	0.05	
Intubation	0.1-0.2	45-90
Relaxation (N_2O+O_2)	0.05	25-40
Relaxation (vapor)	0.03 - 0.04	25 - 40
Maintenance	0.01 - 0.02	15 - 30
Infusion	0.8 - 2.0 µg./kg./min.	



CHEMICAL FORMULA OF ATRACURIUM

Fig 9

ATRACURIUM

Structure : (Fig . 9)

Atracurium is benzylisoquinolinium diester relaxant of intermediate duration of action, emerged from a series of studies by *Stenlake* and *colleagues in the mid 1970's,* that were designed to produce a non-depolarizing relaxant that might undergo 'Hofmann elimination' *(Stenlake JB, Waigh RD, Urwin J et al).*

In this chemical reaction, a cyclic quaternary nitrogen grouping, under the influence of high pH and temperature, opens a tertiary amine. In Atracurium, Stenlake et al. adapted the reaction to a molecule, that not only has good neuromuscular blocking property but also undergoes the reaction at physiologic pH and temperature. This drug was introduced into clinical practice in Britain by *Payne* and *Hughes in 1981,* and in United States by *Basta et al. in 1982.*

Atracurium, like vecuronium is one of the most populor relaxant in clinical practice. As a muscle relaxant of intermediate duration, Atracurium has revolutionized clinical practice. It is the first non-depolarizing blocker to be largely broken down in the blood stream; perhaps the most significant advantage of this agent is its degradation by a chemical reaction (Hofmann elimination) that is not affected by biologic disorders

	Dosage (mg/kg.)	Clinical Duration (min)
E D 95	0.25	
Intubation	0.5-0.6	30-45
Relaxation (N_2O+O_2)	0.3 - 0.4	30-45
Relaxation (vapor)	0.2 - 0.3	30 - 45
Maintenance	0.1 - 0.15	15 - 20
Infusion	4 - 12 µg./kg./min.	

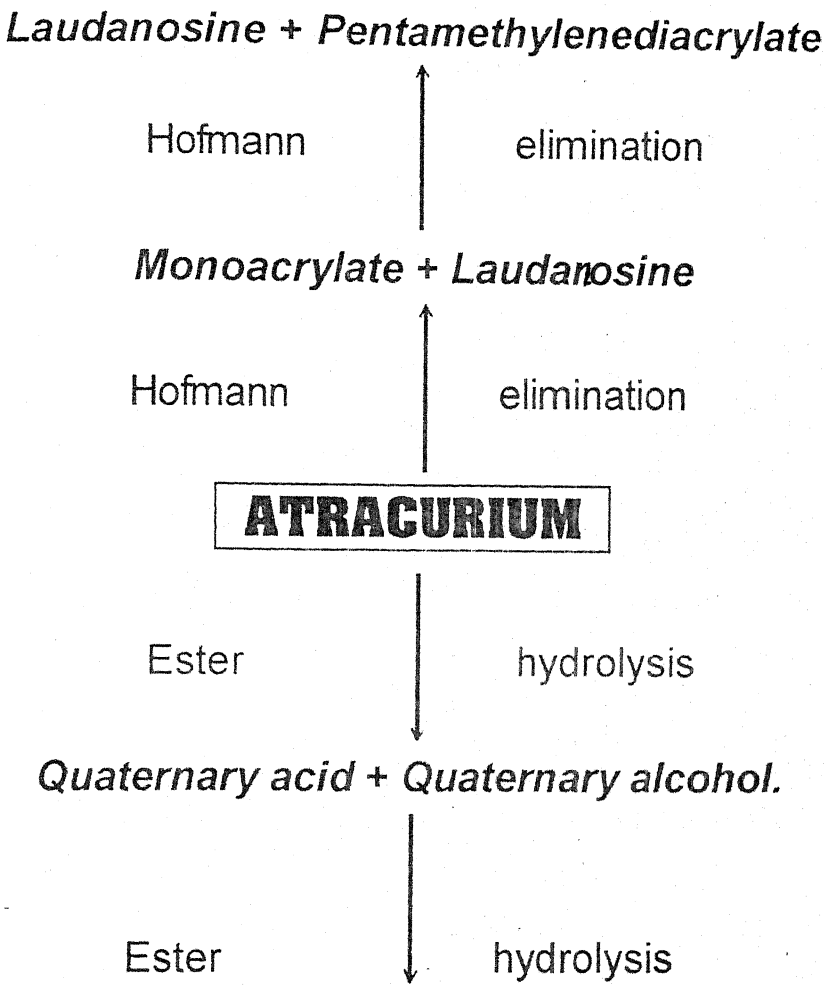
CARDIOVASCULARR SIDE - EFFECTS -

As a benzyl-iso quinolinium compound, Atracurium has the potential for release of histamine. The syndrome becomes clinically evident when doses of 0.5 mg/kg (two times ED 95) or more are injected rapidly *(Basta SJ, Saverese JJ, Ali HH et al, 1983).* When plasma histamine levels increase to over 1000 pg/ml, a transient decrease in blood pressure, together with facial erythema, may be noted. The phenomenon of histamine release may be shifted to the right by a factor of 1.5 to 2.0 by slower injection (30 - 60 sec.). Combined H_1 and H_2 blockade affectively prevents the cardiovascular menifestations of histamine release. Hosking et al. have treated patients with diphenhydramine (1.5 mg/kg or six times the ED 95). Atracurium induced decrease in mean aterial pressure was reduced from 30 mm Hg (37% below base line) in control subject, to 8 mm Hg (10% below base line) in treated patients, despite a 10 to 20 fold increase in plasma histamine levels. Scott et al. obtained similar results in patients pretreated with chlorpheniramine and cimetidine 15 min. before an atracurium dose of 0.6 mg/kg. Atracurium is nonvagolytic and does not block autonomic ganglia *(Hug ies R, Chapple DJ 1981).*

METABOLISM AND ELIMINATION (Fig. 10)

Atracurium is degraded by 'Hofmann elimination' The reaction is purely a chemical process, which is accelerated by alkaline pH and increase in temperature. Infact, pH change during clinical practice, probably has a very little effect on the speed of reaction, where as a decrease in the temperature below 34°C will lengthen the blocking effect considerably.

Some degree of enzymatic ester hydrolysis also probably occurs. *(Marett R, Thompson CW, Webb EW. 1983).* As much as 90 percent of Atracurium may be destroyed in the



DEGRADATION PATHWAYS OF ATRACURIUM

Fig. 10

plasma, with 10 percent or less of the parent drug being excreted in the urine. There is no biliary excretion of atracurium. By contrast, Fischer et al. estimated that as much as 40% of atracurium undergoes organ based elimination.

A major metabolite of this drug, Laudanosine, is a tertiary amine, that can enter the CNS. Very high doses of laudanosine (5-15 mg/kg) may cause CNS excitation in laboratory animals, but no clear cut cases have been noted in humans, even when renal and hepatic failure are present *(Yate-PM, Flynn PJ, Arnold RW et al 1987).*

Consequently, the potential effects of this metabolite of atracurium in the CNS in human subjects are likely to be subclinical, although difficult to determine in the I.C.U. Landonosine is excreted in the urine and bile *(Canfell PC, Castagnoli N, Fahey MR et. al. 1986)*

Materials and Method

MATERIALS AND METHOD

The present study was conducted in the department of Anaesthesiology, M.L.B. Medical College, Jhansi (U.P.) during the year 1996-97, on patients from different surgical specialities, between the age group of 20-60 years, belonging to ASA I and II scheduled for various elective operations.

Selection of patients :-

Subjects for the present study were selected at random, keeping in mind the following criteria :

(1) Patients should be in the age group of 20-60 years.

(2) Sex should be no bar in selecting the patients.

(3) Patients with cardiovascular disease or suffering from systemic disorders other than that for which they were scheduled for surgery were excluded from the study.

(4) Patients suffering from any neuro-muscular disease were not scheduled for the study.

(5) Any history of drug intake, that might influence the pharmacodynamics of neuromuscular blocking drugs, were also not included in the study.

(6) Only those cases where duration of surgery was anticipated to be more than one hour, were accepted.

PRE-ANAESTHETIC CHECK UP :-

All the patients were subjected to detailed preanaesthetic check up including history, general and systemic examination and routine investigations.

Routine investigations required during the study were -

(1) Blood - Hb%
TLC
DLC
ESR
Blood urea
Blood sugar

(2) Urine - Sugar and albumin
Microscopic examination.

(3) Radiological - X-Ray chest.

(4) E.C.G.

Apart from these investigations any specific test if required was also ordered, after proper pre-operative anaesthetic check up, an informed consent of the patient to participate in the study was obtained.

The selected patients were then randomly divided into two groups (50 patients in each group) on the basis of muscle relaxant used.

Gp I- Patients recieved atracurium

Gp II- patients recieved vecuronium.

These two groups were again subdivided into two subgroups of 25 each, according to the technique of maintenance doses used.

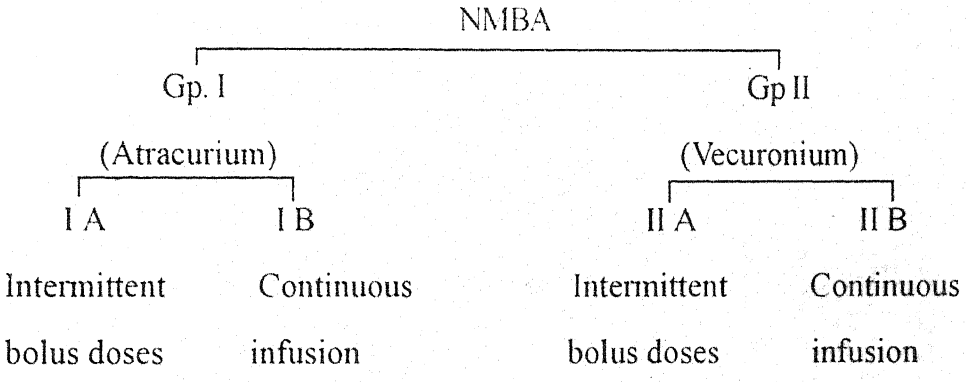
Gp I A- After loading dose of Atracurium 0.5 mg/kg, intermittent bolus doses

of 0.1 mg/kg were given as and when required.

Gp. I B - After same loading dose of atracurium, infusion was started at the rate of 0.45 mg/kg/hr. after 15 min. of loading dose.

Gp. II A - A loading dose of 0.08 mg/kg Vecuronium followed by intermittent bolus doses of 0.015 mg/kg given, as required.

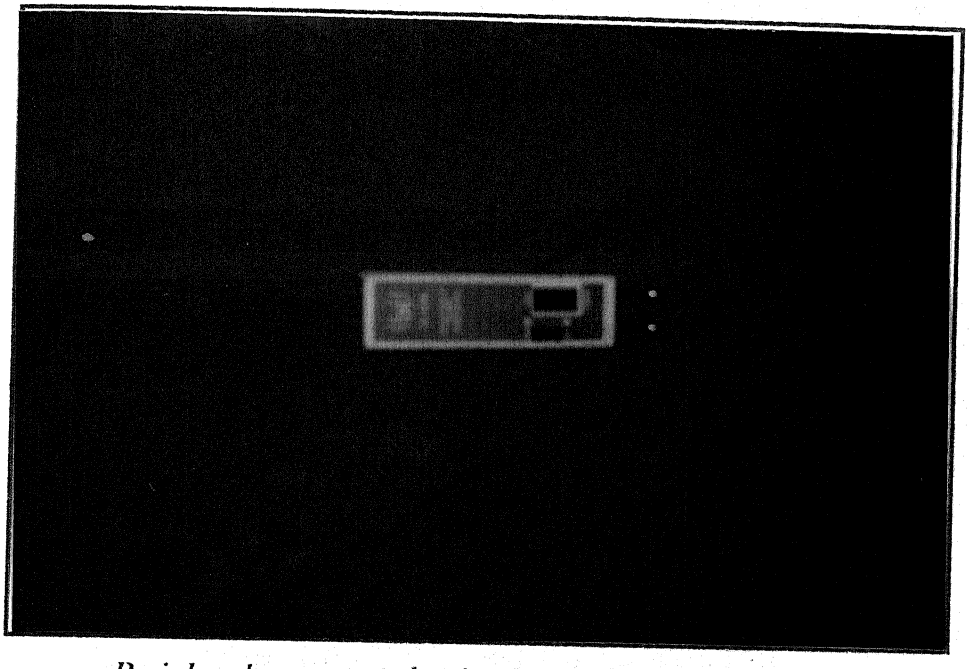
Gp. II B - Loading dose of vecuronium was followed by infusion at the rate of 0.08 mg/kg/hr. after 10 min. of loading dose.



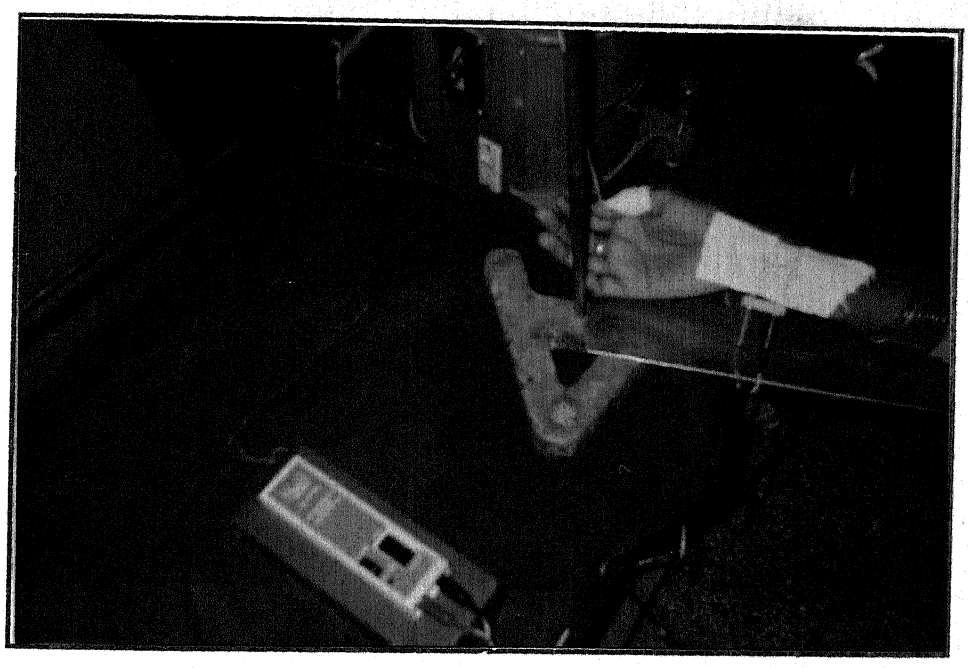
Starting of infusion pump 15 min. after loading dose of Atracurium and 10 min. after loading dose of Vecuronium were based on the fact that duration of action . of loading dose of Atracurium and Vecuronium have been reported to be 30 - 35 min. and 20 min. respectively and starting of infusion at the $t^1/_2$ of drug would maintain a steady plasma concentration.

PRE-MEDICATION :-

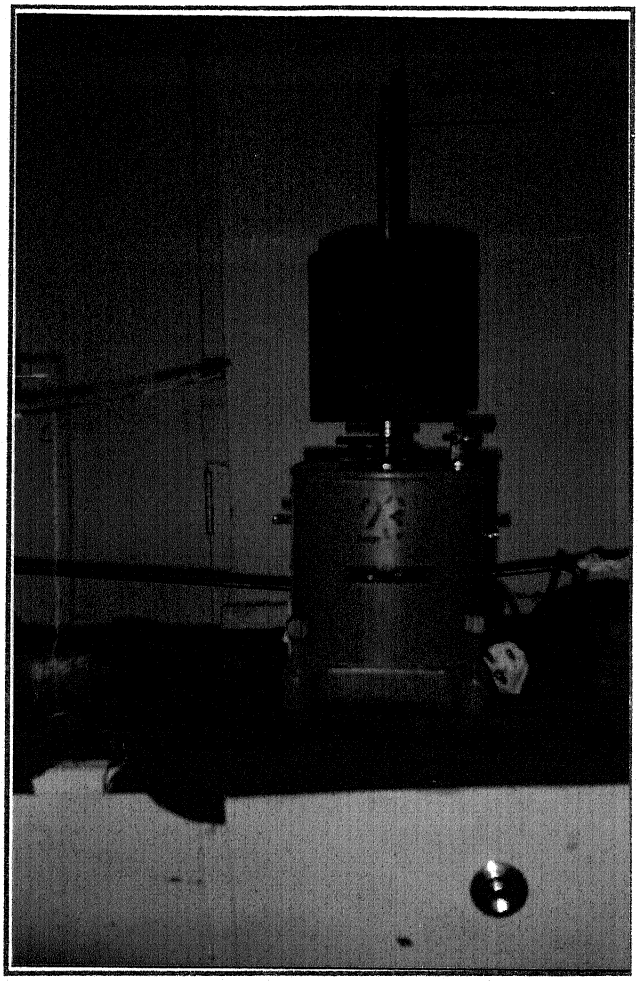
All the patients were kept on fasting for 8 hours and were advised tab. Diazepam 5-10 mg a night before surgery. After obtaining informed consent to participate in the



Peripheral nerve-muscle stimulator - Model AMCA - 100



Nerve - muscle stimulator with electrodes attached at the wrist joint



Kymograph

Starling's heart lever and kymograph assembly attached to the patient's hand to record contractions.

study and consent for the surgery, these patients were premedicated with inj. Glycopyrrolate 0.2 mg., inj. Promethazine 25 mg., inj. Buprenorphine 0.3 mg. i.m. 45 min. prior to the induction of anaesthesia. Basal pulse rate, systolic, diastolic and mean arterial pressure were recorded. I.V. cannulation was performed with 18 gauze cannula under full aseptic precautions. E.C.G. electrodes were connected to the patients.

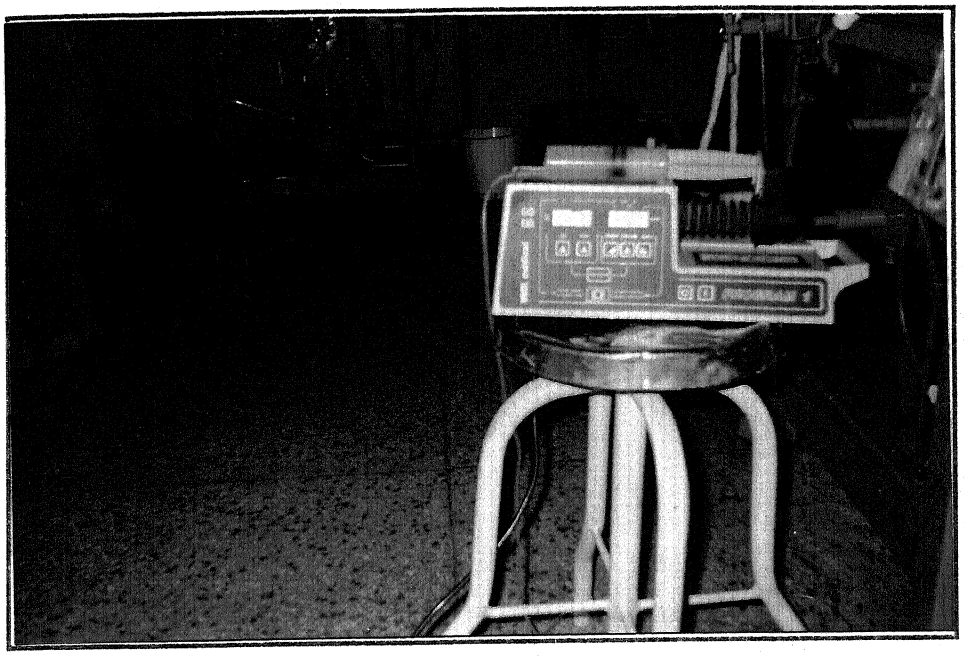
Surface electrodes of nerve-muscle stimulator (AMCA model 100) were applied at the wrist after applying jelly and were firmly secured in place with adhesive tape.

Ulnar nerve at wrist was stimulated at the wrist joint and isometric twitch contraction produced by single twitch was recorded as a control twitch height on a moving drum of Kymograph.

INDUCTION :-

Pre-oxygenation with 100% oxygen was initiated 3-5 min. before induction. Induction of anaesthesia was performed with thiopentone sodium 2.5%, 4-5 mg/kg given intravenously, slowly till the abolition of eye lash reflex, followed by bolus dose of suxamethonium 1.5 mg/kg. IPPV with mask was done with 100% oxygen. When jaw muscles were adequately relaxed, direct laryngoscopy was performed and the patients were intubated with adequate sized cuffed endotracheal tube. Pulmonary entry of air was checked bilaterally, tube was secured in place with tape and cuff inflated. Connections were made to attach from the patient to the Boyles machine through Bain's circuit. IPPV was continued with N_2O and O2 in the ratio of 60% and 40%

When the respiratory excursions were first felt in the reservoir bag, loading doses of Atracurium 0.5 mg/kg. and Vecuronium 0.08 mg/kg were given to the Gp. I & Gp. II patients respectively.



Infusion pump - Vial Medical Program 1 : France.

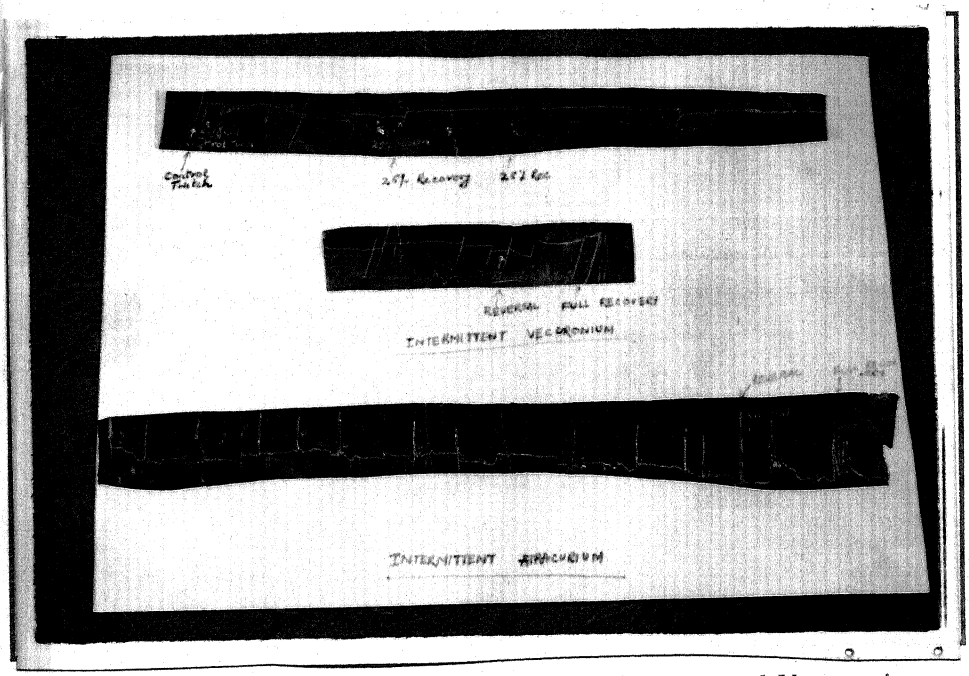
Infusion pump connected to the patient, with neuromuscular relaxant diluted in 50 ml. disposable syringe.

Pulse rate and B.P. were recorded at 2,5 and 10 min. after the loading dose of muscle relaxants. At the same time, onset time (i.e. time from injection to peak effect) was also recorded. Peak effect was judged by suppression of twitch response after single stimuli and depression of all four twitches after four consecutive pulses delivered at 2 Hz. for 2 sec. that is, train of four stimuli.

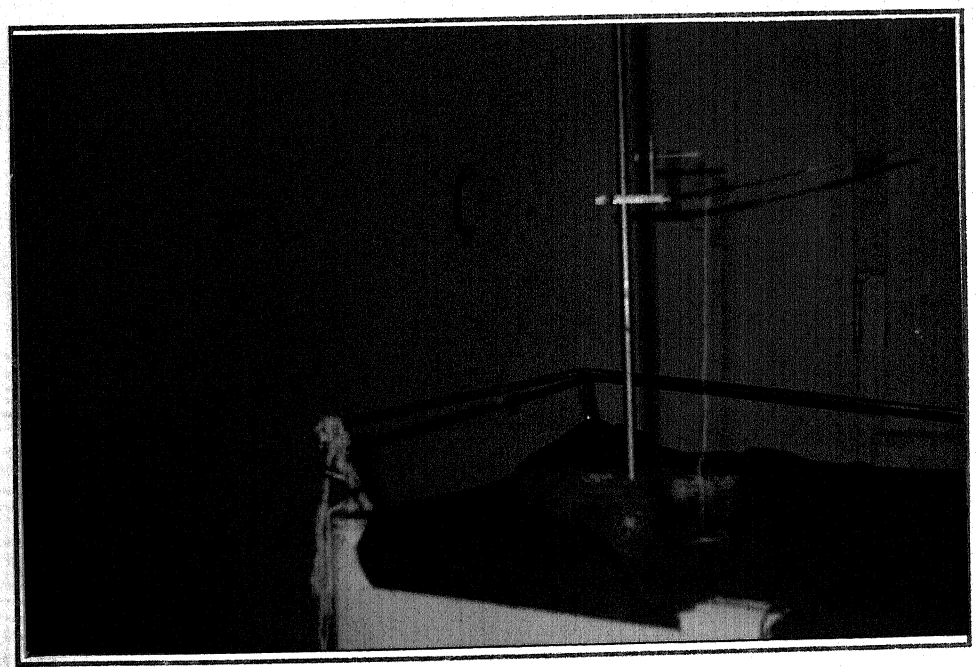
When there was 25% recovery of blockade (as assessed by comparing evoked twitch with control value and by giving TOF stimuli), intermittent bolus doses of Atracurium and Vecuronium were given to Gp. IA and IIA patients respectively and infusion was started 15 min. after the loading dose of atracurium and 10 min. after the loading dose of vecuronium in Gp. IB and Gp II B patients respectively. For infusion **Vial Medical Program I** pump was used. Infusion solutions, used during the study were made by diluting 2.5 ml (25mg) Atracurium or 2 ml (4mg) Vecuronium in 50 ml normal saline. Pulse rate and blood pressure were recorded at 10 min. interval and EKG monitoring was done in lead II through out the surgery. At the same time, any signs of histamine release such as unexplained hypotension., tachycardia, urticaria, rashes or bronchspasm were also noted.

Degree of muscle relaxation was assessed clinically by asking the surgeon and by neuromuscular monitoring and was categorized as excellent, good, or unsatisfactory.

10 min. before the anticipated completion of surgery, infusion pump was stopped. When there was 25% recovery of blockade (assessed by TOF stimuli), patients were reversed with usual doses of neostigmine and glycopyrrolate and patients were extubated after thorough suctioning. Time taken for full recovery was noted. Criteria taken for full recovery were :



Kymographic Tracings of Intermittent Atracurium and Vecuronium



Starling's heart lever

(1) Spontaneous & sustained eyes opening.

(2) Protrusion of tongue.

(3) Head raising for atleast 5 sec.

(4) Ability of patients to follow commands.

(5) By the use of N M stimulator by giving TOF stimuli to see if there was any fade present.

Absence of any of the above mentioned signs were considered as inadequate or partial recovery and any such delay was noted and managed accordingly.

MONITORING :-

(1) Pulse rate

(2) Systolic and diastolic B.P.

(3) E.C.G. monitoring in lead II

(4) Neuromuscular monitoring using single twitch and TOF stimuli.

(5) Any signs of histamine release.

All the above parameters were recorded as follows :-

(1) Before induction (to serve as basal values)

(2) Post intubation.

(3) Before non depolarizer muscle relaxant (N D M R)

(4) 2,5 & 10 min. after loading dose of NDMR.

(5) At every 10 min. through out the surgery.

(6) After reversal.

All the above data were recorded on predesigned proforma by the same observer.

At the completion of study, the results were compiled and analysed statistically using paired 't' test for changes within the group and unpaired 't' test for comparision among groups.

Observations

OBSERVATIONS

On completion of study and analysis, following observations were made and recorded -

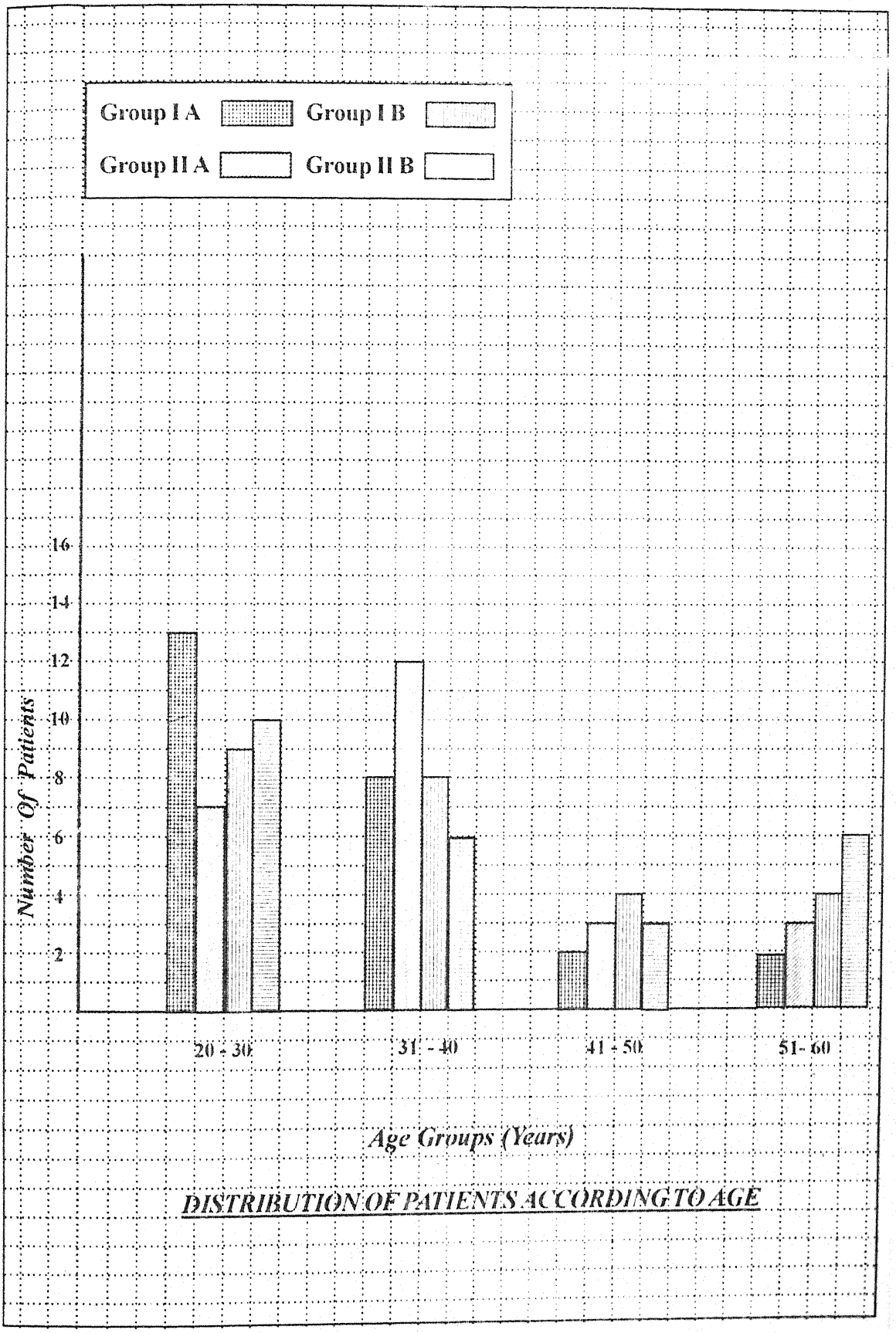
AGE AND SEX DISTRIBUTION

Table I - Distribution of patients according to age and sex.

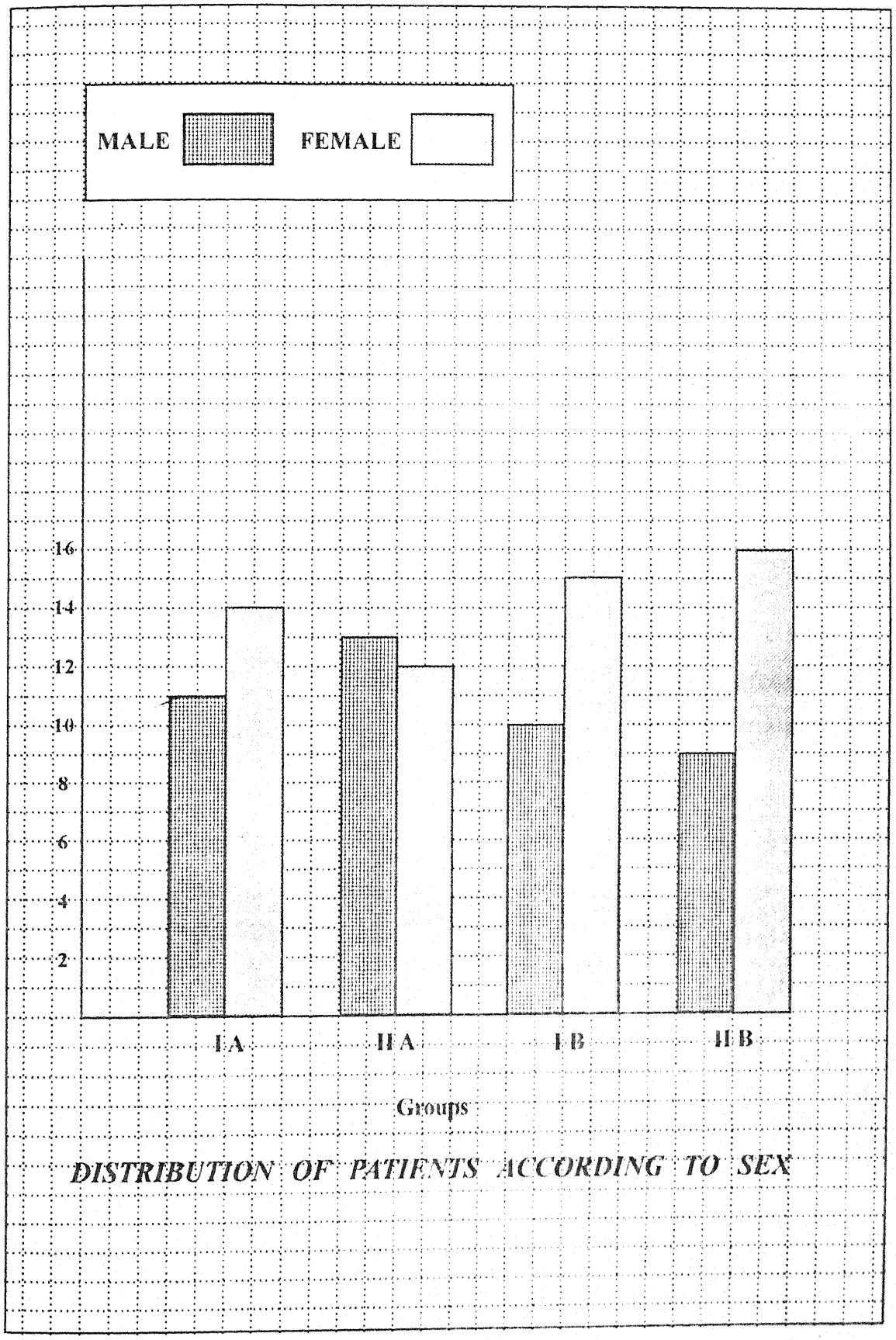
VARIABLES	Gp. IA	Gp. IIA	Gp. IB	Gp. IIB
20-30	13*	07	09*	10*
31-40	08	12*	08	06
41-50	02	03	04	03
51-60	02	03	04	06
Mean Age ± S.D.	32.96 ± 10.93	36.24 ± 10.46	38.48 ± 10.89	38.24 ±13.16
SEX.				
M	11	13	10	09
F	14	12	15	16

*Max number of patients.

Table I shows the number of patients in different age groups. Maximum number of patients were in 20-30 years age group in Gp IA, IB & IIB and 31-40 years age in group II A. Mean age of patients was 32.96 ± 10.93 years in group IA, 36.24 ± 10.43 in group IB, 38.48 ± 10.89 in IIA and 38.24 ± 13.16 in group II B.



DISTRIBUTION OF PATIENTS ACCORDING TO AGE



DISTRIBUTION OF PATIENTS ACCORDING TO SEX

TABLE II :- Showing weights of the patients (Mean ± S.D.)

Group	No. of Cases	Weight (Mean ± S.D.)kg.	Range (kg.)
I A	25	54.12 ± 7.05	42 - 72
II A	25	57.28 ± 8.0	42 - 76
I B	25	58.8 ± 8.93	46 - 82
II B	25	55.04 ± 5.74	46 - 66

Mean weight of patients in group IA was 54.12 ± 7.05, in Gp IIA 57.28 ± 8.0, in Gp. IB 58.8 ± 8.93 and in group IIB, it was 55.04 ± 5.74. Differences in weight of the patients among the four groups were found to be statistically insignificant ($p > 0.05$) (Table II.)

Table III shows the distribution of patients according to type of surgery :-

SURGICAL PROCEDURES	NUMBER OF PATIENTS			
	Gp. I A	II A	I B	II B
ABDOMINAL HYSTERECTOMY	4	2	4	4
VAGINAL HYSTERECTOMY	2	2	4	2
MIDDLE EAR SURGERIES	8	7	7	7
CHOLECYSTECTOMY	2	3	5	3
VESICO VAGINAL FISTULA REPAIR	1	-	-	-
NEPHROLITHOTOMY	3	-	1	-
RADICAL/SIMPLE MASTECTOMY	1	1	-	1
CHOLEDOCHOLITHOTOMY	1	-	1	1
NAILING TIBIA	1	1	-	-
DCP FEMUR / NAILING FEMUR	1	1	-	-
LAPAROTOMY	-	1	1	1
APPENDICECTOMY	-	2	1	4
NEHPHROSTOMY	-	1	-	-
PLATING/NAILING HUMERUS	-	2	-	-
AUSTIN MOORE PROSTHESIS	-	1	-	-
MALLEOLAR SCREW FIXATION	-	1	-	-
STRIPPING VERICOSE VEINS	-	-	1	-
EXCISION NASO PHARYNGIAL ANGIOFIBROMA	-	-	-	1
HELLER'S MYOTOMY	-	-	-	1
NEUROLYSIS RADIAL NERVE	1	-	-	-
TOTAL	25	25	25	25

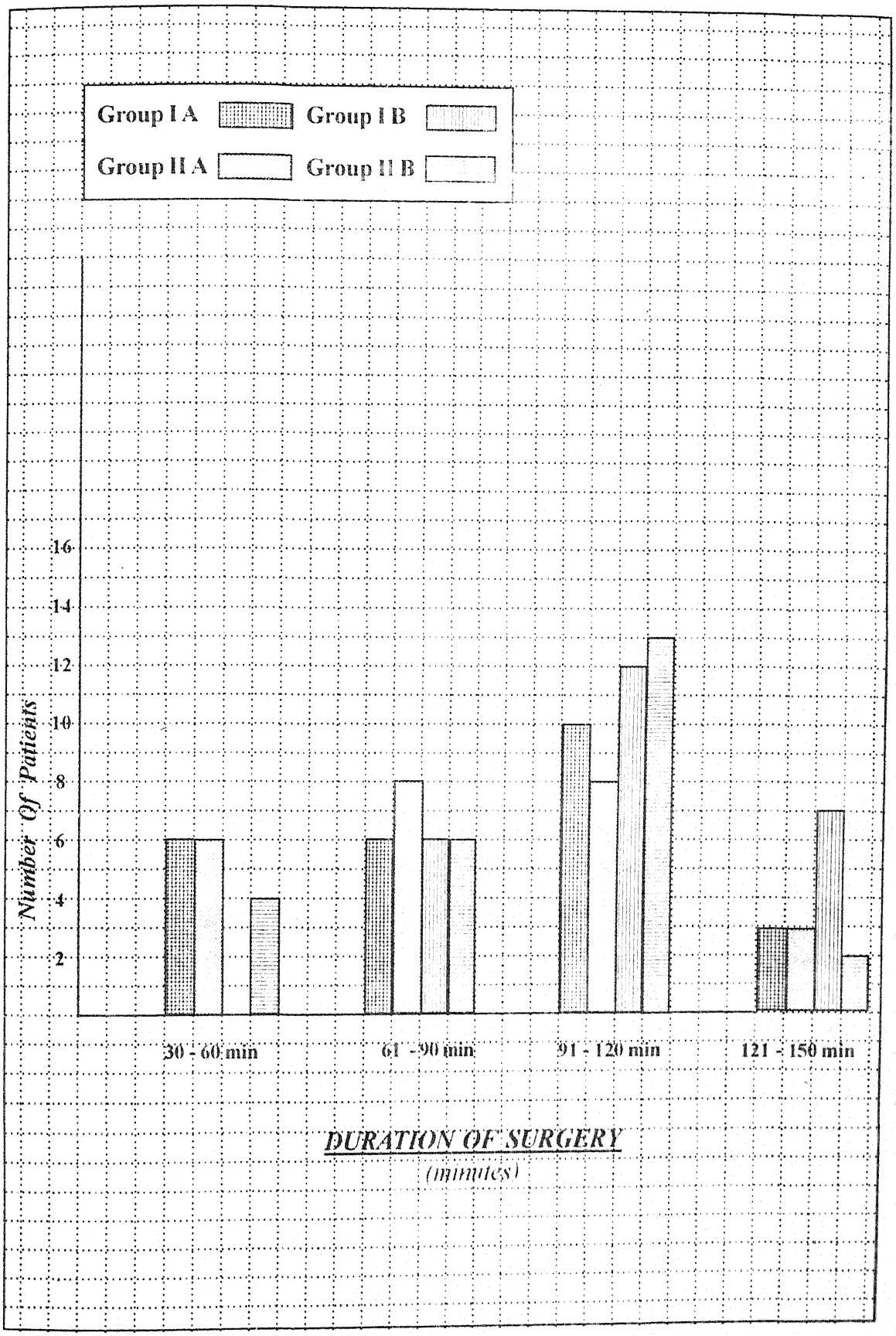

Group I A
Group I B
Group II A
Group II B
Number Of Patients
16
14
12
10
8
6
4
2
30 - 60 min
61 - 90 min
91 - 120 min
121 - 150 min
DURATION OF SURGERY
(minutes)

TABLE IV - Distribution of patients according to duration of surgery (min.)

Total duration (min.)	No. of patients			
	Group I A	IIA	I B	II B
30 min. - 60 min.	6	6	-	4
61 min. - 90 min.	6	8	6	6
91 min. - 120 min.	10	8	12	13
121 min. - 150 min.	3	3	7	2
151 min. - 180 min	-	-	-	-
Mean duration ± S.D.	95.80 ± 30.30 min.	91.2 ± 31.28 min.	111.32 ± 19.15 min.	96.8 ± 23.86 min.

Table IV shows distribution of patients according to the total duration of surgery. Table shows that maximum number of patients in all the groups were in 91-120 min. group. Mean total duration in Gp. IA was 95.80 ± 30.30 min., in II A 91.2 ± 31.28 min. , in group I B 111.32 ± 19.15 min. and in group II B duration was 96.8 ± 23.86 min.

TABLE V : Onset of action of muscle relaxant (inj. to peak effect)

Mean ± S.D. (min)

Group	Onset (min) (Mean ± S.D.)
I A	6.04 ± 0.69
II A	3.93 ± 0.85
I B	6.12 ± 1.73
II B	3.81 ± 0.92

Table V shows mean onset time (i.e. time from injection to peak effect) of muscle relaxant. It was judged by, time from injecting the loading dose of neuro-muscular blocking drug to suppression of all the four twitches, when train of four stimuli was given by nerve stimulator. In group I A & IB (i.e. Atracurium group) mean onset time was 6.04 ± 0.69 and 6.12 ± 1.73 min. respectively, and in group II A & II B (i.e. vecuronium group), it was 3.93± 0.85 and 3.81 ± 0.92 min. respectively.

TABLE VI :- Surgical conditions - Degree of muscular relaxation

SURGICAL CONDITIONS	NUMBER OF PATIENTS							
	I A		II A		I B		II B	
	No.	%	No.	%	No.	%	No.	%
EXCELLENT	22	88%	21	84%	22	88%	20	80%
GOOD	01	4%	02	8%	02	8%	03	12%
ACCEPTABLE	02	8%	02	8%	01	4%	02	8%
UNSATISFACTORY	-	-	-	-	-	-	-	-

Table VI shows surgical conditions i.e. degree of muscular relaxation. It was assessed clinically by asking the surgeons and by suppression of twitches in response to TOF stimuli. Muscular relaxation was excellent in more than 80% cases.

Table VII :- Mean time interval between maintenance doses.

Groups	Mean time	± S.D.
I A	10.68	± 2.13
II A	10.33	± 1.78

Table VII shows mean time interval between mainenance doses in intermittent bolus groups I A and II A. In Atracurium group, intermittent doses had to be repeated at intervals of 10.68 ± 2.13 min. and in group II A, these were required after every 10.33 ± 1.78 min.

This time interval was almost constant between all the maintenance doses and there was no gradual increase in the duration of action.

TABLE VIII : CHANGES IN PULSE RATE :

TIME OF RECORDING	PULSE RATE (MEAN ± S.D.) PER MIN.			
	I A	II A	I B	II B
Pre-operative (Basal value)	83.52 ± 8.14	83.16 ± 6.15	81.76 ± 7.95	85.12 ± 5.25
After intubation	*97.61 ±11.30	*95.2 ±8.80	*93.12 ±6.64	*95.39 ±6.15
After NDNMB at :- 2 min.	** 95.18 ± 6.35	** 98.69 ± 12.11	89.84 ± 8.944	89.44 ± 6.349
5 min.	** 93.9 ± 11.15	** 90.17 ± 11.78	90.08 ± 8.50	88.64 ± 5.188
10 min.	88.66 ± 13.11	87.34 ± 12.11	84.96 ± 6.48	84.96 ± 6.78
30 min.	85.38 ± 7.80	84.59 ± 11.29	88.48 ± 8.69	84.84 ± 6.34
1 hour	82.1 ±7.49	83.78 ±8.11	90.32 ±7.53	83.93 ±6.51
$1^1/_2$ hour	83.25 ± 6.67	82.64 ± 10.43	** 91.74 ± 8.68	89.17 ± 4.75
Before reversal	82.15 ± 11.79	81.78 ± 8.97	** 99.76 ± 8.62	** 103.28 ± 9.22
10 min. after reversal	89.64 ± 7.77	91.39 ± 13.56***	92.64 ± 6.40	94.04 ***± 6.54***

* Significant rise in pulse rate after intubation
** Significant change in pulse rate after NDNMB.
*** Significant change 10 minutes after extubation.

CHANGES IN PULSE RATE

In all the groups, there was a significant rise, after intubation ($P < 0.05$), which persisted even 10 min. after giving non-depolarizer muscle relaxant.

In group IA, pulse rate remained incresed significantly ($P< 0.05$) even at 5 min. after Atracurium loading dose, thereafter it gradually returned to basal values At 1 hr. pulse rate was less than basal values i.e. 82.1 ± 7.49, and before giving reversal, it was 82.15 ± 11.79.

In Gp II A, similar results were obtained, as in case of group I A. At 10 min. pulse rate was 87.34 ± 12.11 per min. (insignificant) ($P > 0.05$), then gradually it returned to basal values. At 30 min. pulse rate was 84.59 ± 11.29 and just before giving reversal, it was 81.78 ± 8.97.

In Atracurium infusion group (IB), there was insignificant change at 2 min. and 5 min. ($P > 0.05$). Pulse rate at 2 min. and 5 min. was 89.84 ± 8.94 and 90.08 ± 8.50 respectively as compared to 81.76 ± 7.95 basal value. At 10 min., 30 min. and 1 hrs., there was insignificant change in pulse rate. Then at 1 $^1/_2$ hr. and before reversal it was 91.74 ± 8.68 and 99.76 ± 8.62 respectively, which was a significant change ($P<0.05$).

In group II B (Vecuronium infusion group) pulse rate at 2 min. after NDNMB was 89.44 ± 6.35 as compared to 85.12 ± 5.25 basal value. At 10 min; pulse rate fell below basal values (84.96 ± 6.78). There was no significant change till 1$^1/_2$ hr when it was 89.17 ± 4.75, but just before giving reversal there was significant rise ($P < 0.05$) as it rose to 103.28 ± 9.22.

10 min after giving reversal, again there was a significant change in all the groups except atracurium intermittent group. In group I A, pulse rate was 89.64 ± 7.79, in group II A 91.39 ± 13.56, Group I B 92.64 ± 6.40 and in group IIB it was 97.04 ± 6.54 per min.

TABLE IX - Changes in Systolic blood pressure

TIME OF RECORDING	SYSTOLIC BLOOD PRESSURE (mm Hg) (Mean ± S.D.)			
	GROUP I A	GROUP II A	GROUP I B	GROUP II B
Pre-operative	119.7 ± 11.75	120.24 ± 10.76	120.56 ± 12.81	123.04 ± 11.74
After intubation	137.84 ± 15.68*	136.64 ± 12.59*	134.48 ± 11.68*	136.62 ± 13.4*
After NDNMB	-	-	-	-
At 2 minutes	135.84 ± 16.55**	134.04 ± 12.48**	132.6 ± 12.48**	134.6±12.11**
5 minutes	128.72 ± 19.64	124.96 ± 10.88	128.64 ± 12.61	127.84 ± 9.79
10 minutes	121.6 ± 13.90	120.41 ± 11.61	124.54 ± 11.88	126.32 ± 10.75
30 minutes	117.84 ± 12.74	122.0 ± 11.79	124.66 ± 10.53	124.47 ± 12.44
1 hour	116.28 ± 16.16	119.09 ± 12.41	126.59 ± 11.31	124.17 ± 12.5
1½ hour	117.76 ± 11.48	120.43 ± 13.48	129.47 ± 10.66	128.18 ± 10.59
Before reversal	118.11 ± 12.16	120.47 ± 10.18	129.6 ± 13.34	133.2 ± 13.71
10 minutes after reversal	118.80 ± 11.41	124.24 ± 10.79	129.76 ± 11.13	132.04 ± 12.84

* Significant rise after intubation ($p < 0.05$)

** Significant change in blood pressure ($p < 0.05$)

CHANGES IN SYSTOLIC BLOOD PRESSURE

In Gp. IA, there was a significant rise in systolic blood pressure ($P < 0.05$) after intubation, when it was 137.84 ± 15.68 as compared to 119.7 ± 11.75 basal value and it remained elevated at 2 min. after giving NDNMB. At 2 min. it was 135.84 ± 16.55 mm Hg, then gradually it returned to basal value and 30 min., 1 hr. and $1^1/_2$ hr. after NDNM drug, values were 117.64 ± 12.74, 116.28 ± 16.16, 117.76 ± 11.48 respectively. After reversal, systolic B.P. in this group was 118.80 ± 11.41.

In vecuronium intermittent gp. ((IIA) basal value of systolic B.P. was 120.24 ± 10.67. After intubation, there was a significant rise ($P < 0.05$), when the value was 136.66 ± 12.59 and at 2 min. after giving loading dose of vecuronium, it was 134.04 ± 12.48. There after it returned close to its original value. At 10 min., 30 min., 1 hr. and $1^1/_2$ hr., the values were 120.41 ± 11.61, 122.0 ± 11.79, 119.09 ± 12.41 and 120.43 ± 13.48 respectively 10 min. after reversal systolic B.P. in this gp. was 124.24 ± 10.79 mm Hg.

In Atracurium infusion gp. (IB), systolic blood pressure rose significantly to 134.48 ± 11.68. Then it fell down to 124.66 ± 10.53 mm Hg at 30 min. after infusion and remained almost constant till one hour of surgery. At $1^1/_2$ hr & before reversal it was 129.47 ± 10.66 & 129.6 ± 13.34 resp. . After reversal systolic B.P. was 129.76 ± 11.13.mm Hg.

In vecuronium infusion group (IIB) basal systolic value was 123.04 ± 11.74 mm Hg and after intubation it was 136.62 ± 13.4 mm Hg (Significant rise) ($P < 0.05$), Gradually it came down to 127.84 ± 9.79 mm Hg at 5 min. after loading dose and 124.47 ± 12.44 & 124.17 ± 12.5 at 30 min & 1 hr. after infusion. Just before reversal B.P. was 133.2 ± 13.71 and 10 min. after reversal it was 132.04 ± 12.84.

TABLE X - Changes in Diastolic blood pressure (mm Hg)

TIME OF RECORDING	DIASTOLIC BLOOD PRESSURE (mm Hg) (Mean ± S.D.)			
	GROUP I A	GROUP II A	GROUP I B	GROUP II B
Pre-operative	79.28 ± 7.63	78.60 ± 6.35	80.48 ± 7.74	82.88 ± 5.54
After intubation	84.96 ± 8.78	83.44 ± 8.74	82.96 ± 6.14	83.76 ± 6.59
After NDNMB	-	-	-	-
At 2 minutes	84.03 ± 6.35	83.28 ± 10.12	84.76 ± 9.39	86.64 ± 8.81
5 minutes	83.04 ± 7.81	82.0 ± 6.53	83.84 ± 7.54	86.16 ± 7.81
10 minutes	80.8 ± 9.76	80.81 ± 10.72	78.79 ± 8.51	82.16 ± 6.34
30 minutes	81.43 ± 6.51	80.61 ± 6.59	81.13 ± 6.59	83.29 ± 7.89
1 hour	79.42 ± 7.17	78.8 ± 5.49	79.61 ± 7.68	84.16 ± 5.64
1 & 1/2 hour	80.63 ± 5.48	78.68 ± 9.14	80.11 ± 6.16	84.46 ± 5.44
Before reversal	79.48 ± 6.16	79.69 ± 8.14	79.61 ± 7.68	83.19 ± 6.67
10 minutes after reversal	80.15 ± 4.19	80.59 ± 80.97	83.12 ± 9.63	82.55 ± 5.88

TABLE X shows changes in diastolic blood pressure. There were no significant changes in any group. Diastolic blood pressure remained almost constant throughout the surgery and 10 min. after reversal or there was insignificant change ($P > 0.05$). in

CHANGES IN DIASTOLIC BLOOD PRESSURE

TABLE XI - Changes in Mean Arterial pressure (mmHg.)

TIME OF RECORDING	Mean Arterial Pressure (mm Hg) Mean ± S.D.			
	GROUP I A	GROUP II A	GROUP I B	GROUP II B
Pre-operative	97.11 ± 8.69	95.89 ± 7.23	93.83 ± 6.78	94.46 ± 6.61
After intubation	103.35 ± 9.79	108.95 ± 10.47	99.25 ± 7.81	100.38 ± 8.18
After NDNMB	-	-	-	-
At 2 minutes	101.27 ± 7.33	99.91 ± 8.68	97.87 ± 8.71	99.19 ± 6.89
5 minutes	98.26 ± 8.78	96.58 ± 13.49	97.81 ± 8.69	94.55 ± 7.78
10 minutes	94.71 ± 9.61	93.99 ± 10.78	99.92 ± 9.41	97.71 ± 8.89
30 minutes	93.18 ± 11.66	93.43 ± 8.56	96.79 ± 7.76	96.45 ± 6.54
1 hour	97.0 ± 12.31	88.76 ± 10.7	96.55 ± 5.39	97.32 ± 8.85
$1^1/_2$ hour	95.18 ± 8.49	91.94 ± 9.31	95.69 ± 6.34	97.8 ± 9.05
Before reversal	94.35 ± 9.78	93.19 ± 7.78	98.39 ± 7.78	100.5 ± 6.68
10 minutes after reversal	94.21 ± 11.34	96.18 ± 8.66	102.53 ± 9.93	100.23 ± 6.65

TABLE XI shows changes in MAP (mm Hg). Pre-operative values in IA, II A, I B and II B were 97.11 ± 8.69, 95.89 ± 7.23, 93.83 ± 6.78 and 94.46 ± 6.61 mm Hg. resp.. In II A there was a significant change after intubation when MAP was 108.95 ± 10.47 ($p < 0.05$). There was no significant change in mean arterial pressure in any group during whole surgery and 10 min. after reversal.

CHANGES IN MEAN ARTERIAL PRESSURE

Histamine release :- Gp II A patients showed clinically and statistically insignficant rise in pulse rate but conclusive signs of histamine release viz. unexplained tachycardia in the presence of hypotension, urticaria, rashes or bronchospasm etc. were not seen in any case in any group during entire surgery.

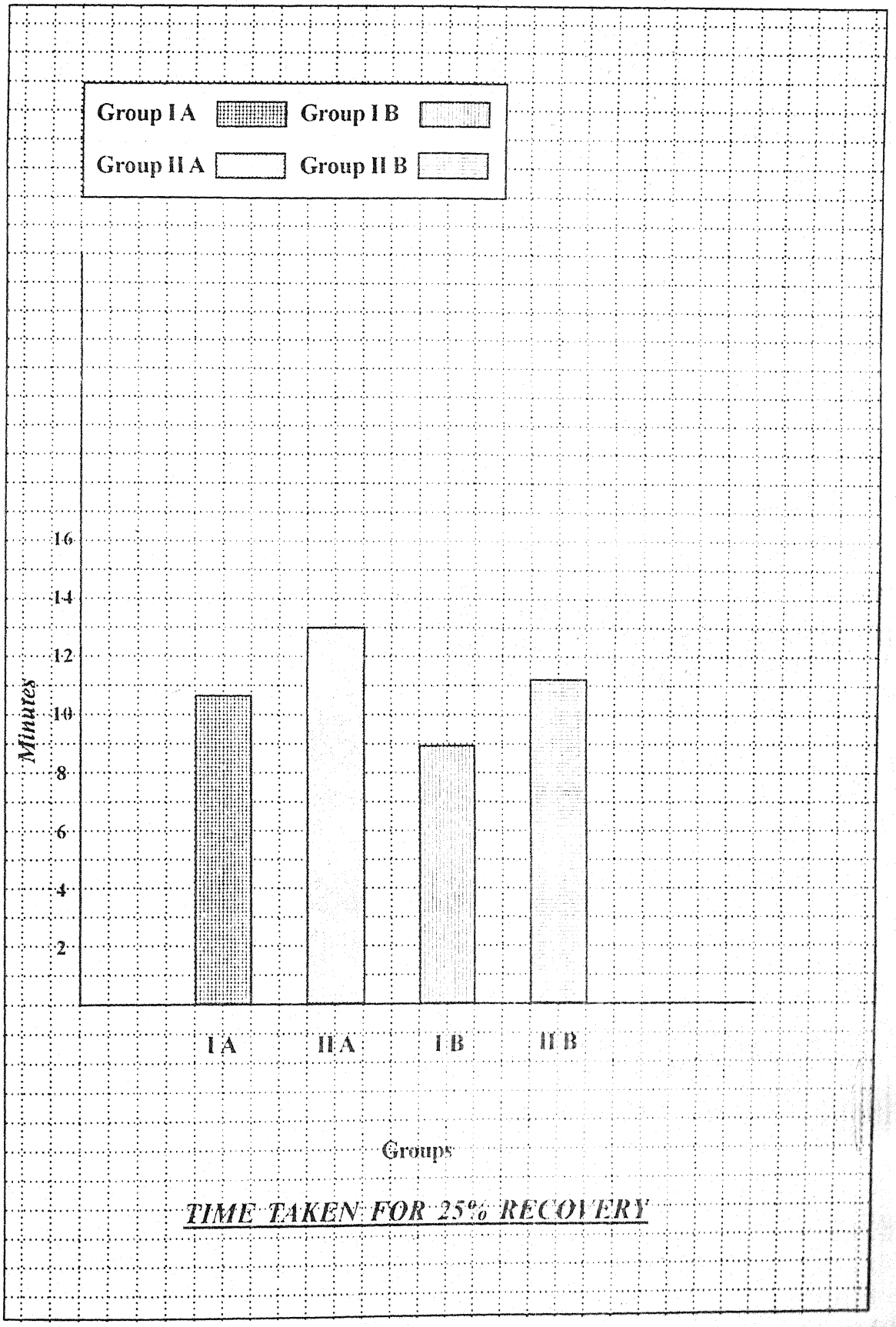
E.K.G. Ghanges :-

In all the patients of ASA Grade I & II. intraoperative EKG montoring was done in Lead II and there were no changes in any group suggestive of any adverse effect by both Atracurium and vecuronium.

TABLE XII : Time from last dose of relaxant or from stopping infusion to 25% recovery of blockade:

Groups	Time taken for 25% recovery (Mean ± S.D.) (min.)
I A	10.44 ±1.63
II A	12.92 ± 2.38
I B	8.96 ± 2.12 min.
II B	11.12 ± 2.25 min.

Table XII shows time taken from last dose of muscle relaxant in intermittent bolus groups and from stopping infusion in infusion groups to 25% recovery of neuromuscular blockade, as assessed by giving TOF stimuli. Time taken for 25% recovery in Atracurium intermittent and infusion group was 10.44 ± 1.63 min. and 8.96 ± 2.12 min. respectively. While in Vecuronium intermittent bolus and infusion groups it was 12.92 ± 2.38 min. and 11.12 ± 2.25 min respectively.



TIME TAKEN FOR 25% RECOVERY

Table : XIII : Time from reversal to full revocery :

Groups	Time for full recoery (Mean ± S.D.) (min)
I A	8.88 ± 1.38
II B	10.8 ± 2.2
I B	9.04 ± 1.71
II B	14.12 ± 3.11

Table XIII shows time taken from injecting reversal in usual doses to full recovery (as judged by clinical signs and by giving TOF stimuli). In gp. IA it was 8.88 ± 1.38 min., in gp. II A time taken was 10.8 ± 2.2 min., in gp IB 9.04 ± 1.71 min. and in group II B patients took 14.12 ± 3.11 min. to recover fully. In the post operative period, all the patients were fully conscious and there were no signs of any cumulation or recurarization or any other complications.

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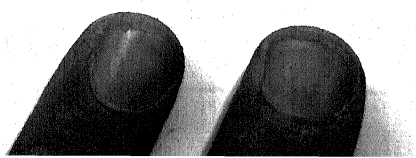

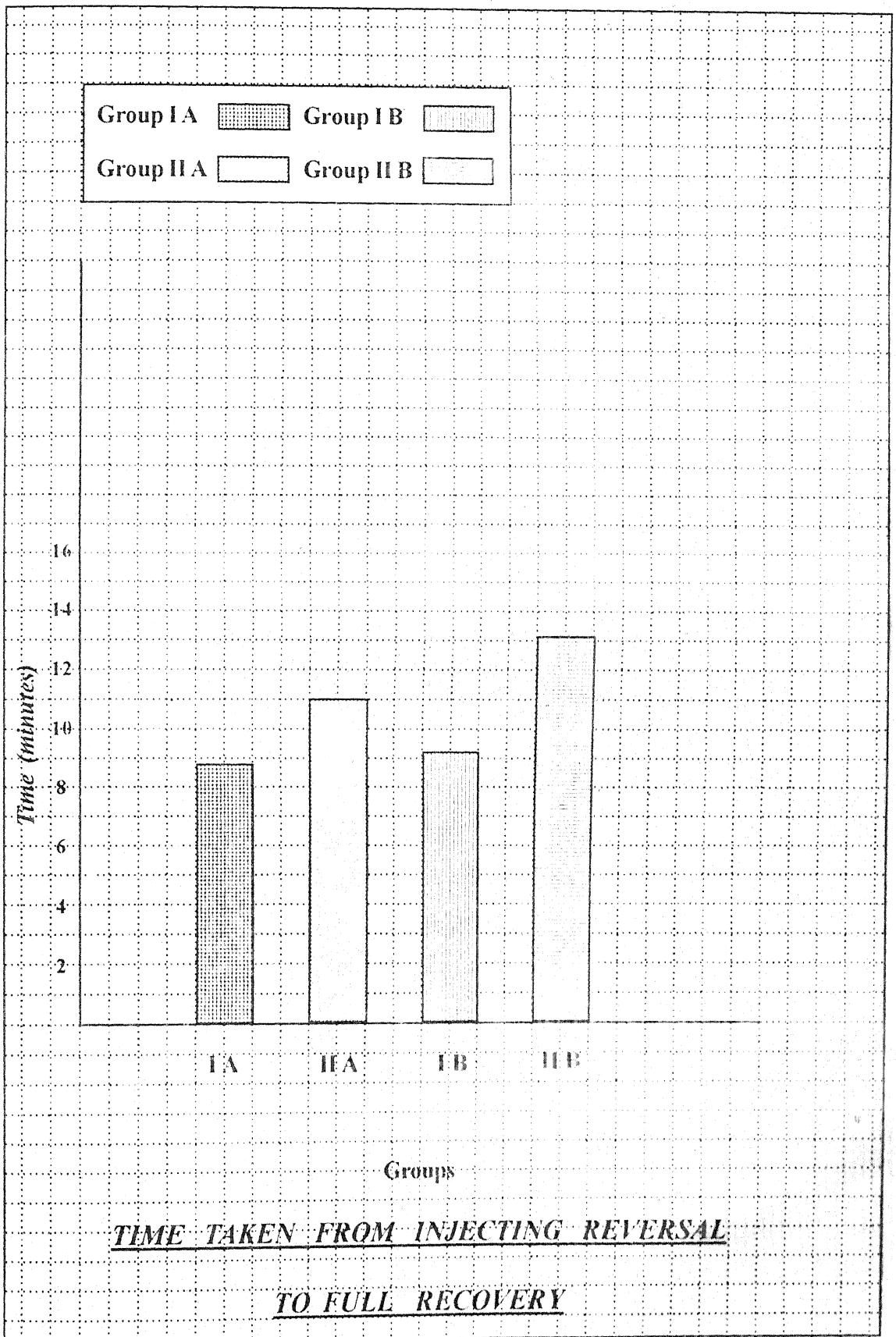

TIME TAKEN FROM INJECTING REVERSAL

TO FULL RECOVERY

Discussion

DISCUSSION

With the rememberance of anaesthesia, during 1930s, and 40s, the statement, that modern anaesthesia owes its existance to the introduction of muscle relaxants in clinical practice, can not be disagreed upon. Hence it would not be out of order, if one can say that the use of curare in 1942, by Griffith and Johnson at Montreal, marked the dawn of modern anaesthesia.

The initial success of curare led, in the subsequent years, to the introduction of many synthetic and semisynthetic neuromuscular blocking agents, which were soon dropped like hot potatoes, blaming them not to be as safe as were previously thought. This was due to the fact, that there was a significantly higher mortality rate in patients recieving these drugs, a finding which was startling to the world and led to a lot of controversy.

An inharent drug toxicity was thought to be the cause as ascribed by *Beecher*. However with the present understanding of neuromuscular blocking mechanism, a possible explaination to this high mortality rate, could be the then unrecognized residual paralysis, leading thereby to post-operative respiratory insufficiency, coupled with non-realization of the importance of antagonism of these drugs.

The above explaination gains its support from the fact that subsequent understanding of the importance of maintenance of adequate pulmonary ventilation during neuro-muscular blockade and its antagonism by neostigmine led to a

tremendous fall in the mortality rate following these drugs and thus the concept of "balanced anaesthesia" came into being. But with the use of neuro-muscular blockers, surgeons also complained of unsteady muscular relaxation during the surgical period, leading to frequent repetition of maintenance doses. Simultaneously; as the scope for anaesthesiologists was increasing in the intensive care units; this also demanded requirement of these drugs for prolonged periods, in patients who were kept on ventilators. Once again a hunt was on, to synthesize more safe drugs, in terms of shorter duration of action, no organ specific adverse effect and no organ - dependent elimination from the body, so that they could be given by continuous infusion method, to achieve a constant plasma level, throughout the surgery, with no residual paralysis after the cessation of their use and rapid recovery.

Many pharmacodynamic models were developed to evaluate safety and efficacy but only Atracurium and Vecuronium could prove their merits, considering their shorter duration of action, no systemic side effects and no residual action after being used by continuous infusion. *(Margaret A Gargarian, Salvatore J. Basta, Saverese J. John. 1994; Mirakhur R.K., Ferres C.J., Pandit S.K. : 1984).*

During the present study, Atracurium and Vecuronium were chosen to provide muscle relaxation, because they have been shown to possess most of the properties of an ideal neuro muscular blocking agent.

The study was designed to minimize interacting influences such as med cal status, premedication, anaesthetic drugs, surgical manipulations and duration of surgery (Table III & IV)

The mean age and weight of the patients were similar in all the groups. (Table I & II).

On set of action (Table V)

The onset of action in Atracurium intermittent bolus and continuous infusion groups (i.e. I A and II A) was 6.04 and 6.12 min. respectively, while in vecuronium II A and II B groups, this was significantly shorter (3.93 and 3.81 min. respectively).

It is worthwhile to mention here that this onset time (i.e. from injection to the peak effect) was noted, after a loading dose of 2xED95 and peak effect was judged by suppression of all four twitches in response to TOF stimuli, which was measured by ulnar nerve stimulation at the wrist.

E.N. Robertson, L.H.D.J. Booij, R.J. Fragen and J.E. Crul (1983) reported onset time for vecuronium and atracurium 4.7 min. and 6.7 min respectively when the drugs were used in the doses of 1xED90, where as it was 2.5 to 3.5 min in a dose of 3xED90. A possible explaination to this discrepency can be that the time to develop maximum blockade at peripheral sites is more than that provided by these agents to facilitate intubation, as the vocal cord relaxation is seen much earlier than the peripheral suppression of all four TOF stimuli, more over these workers had used 3xED90 doses to evaluate the intubating condition, as against 2xED95 during the present study.

G.Noeldge, H.Hinsken and W.Buzello (1984) have reported onset time of vecuronium 3.4 ± 2.4 min after a loading dose of 0.075 mg/kg.

SURGICAL CONDITIONS

These were assessed both clinically and by visualizing suppression of twitches in response to TOF stimuli, Muscular relaxation was excellent in more than 80% of cases in all the groups (Table VI).

During the present study, it was noted that although, the time interval between any two maintenance doses in all the cases, was almost constant (10.68 min. in IA and 10.33 min in II A), thereby showing no cumulative property of these agents, (Table VII), but condition provided by intermittent bolus groups were not constant. There was waxing and waning of muscular relaxation with the recovery of blockade, as was also shown by return of response to TOF stimuli, thus demanding for frequent repetition of maintenance doses of non-depolarizing agents in their respective groups, where as in group IB and II B, there was constant suppression of twitches in response to TOF and a steady state of muscular relaxation was achieved. Thus as the continuous infusion was started 10 to 15 min. after the loading dose, this probably provided constant plasma levels and better surgical conditions as compared to intermittent bolus groups, where plasma concentration was fluctuating and surgical conditions were not stable.

E.N. Robertson and R.J. Fragen (1983) compared atracurium and vecuronium given in the doses of 3xED90 and concluded that blocks produced by these were 85.3 ± 4.0 and 90.9 ± 2.5 %.

The present study also confirms the suggestions of previous studies that time required to stabilize neuro-muscular blockade depends on the loading dose, on the time interval between loading dose and commencement of infusion and on the rate of infusion . It has been suggested by previous workers that as a basic approach, for stable 90% block the loading dose should be in the order of 1.5-2x ED 90, the same dose should be infused per hour and infusion should be started within first 10-15 min. after injecting the loading dose- *(G.Noeldge, H. Hinsken and W.Buzello 1984).*

CARDIOVASCULAR PARAMETERS-

Pulse rate, systolic and diastolic blood pressures and mean arterial pressure (i.e. Diastolic + 1/3 of pulse pressure) were compared at different intervals after the administration of atracurium and vecuronium intermittently or during infusion.

Changes in Pulse rate (Table VIII)

A marked rise in the pulse rate, by a margin of 14%, was observed in all the cases following intubation, during the present study. This beyond doubt, was a normal response to laryngoscopy and intubation. and 10 min after which a fall was recorded, till it came down to its basal value at the 30th minute. However after 1 hr., a decrease by 2-3% was observed in groups IA and IIA & IIB. Surprisingly, this decrease was not seen in group IB, where it remained elevated by the same margin.

An interesting finding noted during the study was that there was again a rise in pulse rate at $1^1/_2$ hrs., and before reversal in both the infusion groups. This rise was not seen in intermittent bolus groups.

Atracurium and vecuronium have been found to be free from direct cardio-vascular responses. The lack of any chronotropic effect with these drugs may allow the heart rate to decrease. However intra-operative bradycardia after vecuronium has been described by *Salmenpera et al. (1983)* and it was thought to result from lack of antagonism of vagotonic influences such as anaesthetic drugs or surgical maneuvers. Similar findings have also been reported by *Barnes et.al. 1982, E.N. Robertson, L.H.D.J Booij and R.J. Fragen in 1983.* But these workers did not find any increase in pulse rate after atracurium.

Although there can be many causes of increased heart rate intra-operatively, the possible explaination to this finding during the present study, could be, that although there were no conclusive evidences, but possibly slight histamine release was there, which was sufficient to increase the pulse rate but was not enough to cause clinically evident syndrome of histamine release. Various workers have reported that this syndrome might become evident clinically when histamine levels increase to over 1000 pg/ml. (details under the subtitle histamine release). Probably these high levels were not achieved during the present study and therefore all other

signs and symptams of histomine release were not seen. But as it is a possibility with the use of atracurium, the subject needs further studies and evaluation.

Increase in pulse rate at 1½ hrs. and just before reversal in infusion groups could be explained by the fact that in most of the cases as the surgery was near its completion and infusion pump was stopped 10 min. before anticipated time of completion, a gradual recovery from the blockade resulted in an increase in heart rate.

CHANGES IN BLOOD PRESSURE AND MEAN ARTERIAL PRESSURE : (Table IX, X & XI)

As with the pulse rate, a 10 - 13% increase in systolic blood pressure and 6-10% increase in mean arterial pressure was observed in all the groups after intubation which may be regarded as a normal response to laryngoscopy and endotracheal intubation. Pressures remained elevated till 5 min. after the loading doses of relaxants in their respective groups. After incremental doses and starting infusion i.e. after 10 to 30 min., systolic blood pressure returned to its basal value or their was 1-2% decrease as compared to preoperative recordings and then it remained almost constant throughout surgery. Similar values were obtained for mean arterial pressure. In both the infusion groups a slight increase in systolic blood pressure was recorded at $1^1/_2$ hr. and before reversal. These findings were parallel to changes in pulse rate and thus confirmed that it was due to gradual recovery of blockade as the infusion was stopped by this time.

These findings coincide to *Lavery et. al. (1987)* who concluded that vecuronium caused no significant changes in systolic blood pressure & mean arterial pressure.

Booij, Fragen and Crul (1987) have also reported no significant changes in heart rate and arterial pressures with atracurium and vecuronium. In their study,

there was statistically significant decrease in mean arterial pressure but this was small (4-5%) and was not considered clinically significant. Similar alterations have also been noted by *Barnes et al. in 1982.*

E.K.G. CHANGES :-

E.K.G. changes in lead II were compared in Atracurium & Vecuronium intermittent bolus groups and infusion groups and it was found that both the drugs caused no abnormality in cardiac rate or rhythm. As these agents have been found to be relatively free from direct cardiovascular action, these agents can be considered safe in relation to any cardiac adverse effects. These conclusions are coincidental with those of *Booij L.H.D.J., Edwards R.T., Sohn Y.S. and Miller R.D. 1981 and Bowman W.C. 1982.*

HISTAMINE RELEASE :

Conclusive signs of histamine release, for example, unexplained slight to moderate rise in heart rate with erythema of the face, neck and upper torso, rashes, fall in arterial pressure and bronchospasm were not found in any case during the study. In Atracurium infusion group slight rise in pulse rate was noted in the absence of any other obvious cause, which may be because of slight release of histamine but no other signs were noted. Vecuronium is virtually free from histamine releasing property. It has been shown that it does not release histamine throughout a wide clinical dose range from one to eight times the ED95 (i.e. 0.05 to 0.40 mg/kg). *Morris R.B., Cahalan M.K., Miller R.D. et. al, 1983, Tullock W.C., Diana P., Cook D.R. et al., 1990)*

Although Atracurium, as a benzylisoquinolinium compound may cause histamine release, *Hughes and Chapple (1981)* reported that Atracurium caused clinically evident histamine release only when 8-16 times the neuro-muscular blocking dose was used intravenously. Duing the present study, there was no clinical evidence of histamine release after the injection of drug.

According to *Basta S.J. (1990), Saverese JJ and Ali H.H. et al (1983),* the syndrome of histamine release may become clinically evident when doses of two times ED95 or more are injected rapidly. When plasma histamine levels increase to over 1000 pg/ml, a transient decrease in blood pressure, together with facial erythema may be noted. This can be prevented by slower injection of atracurium over 30-60 sec. and by the use of combined H_1 and H_2 receptor blockade *(Hoskin et al. 1988). Scott et al (1985)* have also suggested similar findings.

RECOVERY OF BLOCKADE (Table XII & XIII) :-

The time taken from last intermittent bolus dose or from stopping the infusion to 25% recovery of the blockade was 10.44 ± 1.63 sec. & 8.96 ± 2.12 sec. respectively in Atracurium (IA & IB) groups and 12.92 ± 2.38 & 11.12 ± 2.25 sec. respectively in groups IIA & IIB while that taken for full recovery from reversal in its usual dosage was 8.18 sec and 10.8 sec in groups IA and IB respectively and 9.04 and 14.2 sec. in corresponding vecuronium groups. Thus the time for full recovery was significantly more in vecuronium infusion group. There were no signs of residual blockade or recurarization in any case.

The pharmacodynamics of Atracurium and Vecuronium correspond to previously reported studies by *Payne &Hughes (1981) and Crul & Booij (1980).* The reproducible recovery rate of Atracurium, found in the present study, has been commented on before *(Payne & Hughes 1981; Hughes & Chapple 1981).* The prolongation of the recovery rate of Vecuronium has also been noted in other studies *(Agoston et al, 1980)* but has been considered to be insignificant. If Vecuronium terminates its effects by redistribution, as suggested by several pharmacokinetic studies *(Agoston et al, 1977; Booij et al 1981),* the prolonged recovery rate might suggest that the distribution volume is becoming saturated at these doses. If even greater doses of vecuronium were used, the increase in the duration of recovery may

lead, possibly to prolongation of the total duration of action. In contrast the steady recovery rate of Atracurium might suggest that the metabolic pathways thought to terminate its effects (Hofmann elimination and ester hydrolysis) are not saturated at the doses, used.

Sohn and colleagues (1982) proposed a three compartment pharmacokinetic model where the uptake of the unchanged vecuronium was the main priniciple controlling the recovery of neuromuscular transmission, and it may be assumed that the infusion provides a more effective saturation of the third compartment than do intermittent injections. *d' Hollander and colleagues* (1982) observed stable neuromuscular blockade 40 min. after the injection of the loading dose and only 9 ± 4 min. elapsed from the end of infusion until recovery of 25% of control twitch tension. The results with the infusion of atracurium were similar to the findings with the continuous administration of Vecuronium in study carried out by d' Hollander in 1983, except for the recovery time which was 7 min. shorter with atracurium than with vecuronium. This difference may be a result of their different metabolic disposition. Hofmann elimination is the major metabolic pathway controlling the duration of action of Atracurium *(Hughes & Chapple 1981)*. In contrast, Vecuronium undergoes redistribution and excretion with very little metabolic degradation *(Sohn et al. 1982)*. Apparently, under the conditions of continuous infusion, the metabolic pathways of Atracurium are more effective in rapidly restoring neuro-muscular transmission than with Vecuronium.

It can therefore be said that both atracurium and vecuronium have provided the modern anaesthesiologists with the very precious tool to their already vast armamentarium, as is evident by their safe pharmacodynamics over wide ranges of dosage. These drugs no doubt have a promising horion, particularly with their use as continuous infusion.

Conclusion

CONCLUSION

On completion of the study and analysing the observed data, it was concluded that-

1 Onset of action i.e. injection to peak effect was shorter with vecuronium than with atracurium.

2 Both agents provided similar surgical conditions. Muscular relaxation, achieved with the use of atracurium and vecuronium was excellent when these agents were given in the doses of 2-3 times ED 95.

3. Continuous infusion was found to be better method in providing steady surgical condition as compared to intermittent bolus technique, where fluctuations in the degreeof muscular relaxation was observed.

4 Atracurium and vecuronium both have very good cardiovascular stability. Both agents have no direct effect on cardiac rate, rhythm, systolic, diastolic and mean arterial pressures.

5. Vecuronium has no effect on the histamine release, even when used in the doses upto 3 x ED95, while with atracurium, histamine release is rare but a potential complication.

6. Both drugs are safe when used by continuous infusion. Recovery is earlier with atracurium than with vecuronium, which in turn is clinically insignificant.

7. Recovery with both the drugs was spontaneous, with no cumulation.

Therefore, in the end, it was concluded that Atracurium and Vecuronium are shorter acting. No one agent was superiour to another. While atracurium has the

advantage of spontaneous degradation and no organ dependent elimination, vecuronium provides better haemodynamic stability as it is virtually free from histamine releasing property and onset of action is earlier than atracurium.

Their use by continuous infusion is a better alternative to intermittent bolus technique during prolonged surgeries. Although histamine release with prolonged continuous use of Atracurium may be a potential danger.

Both drugs are free from direct cardio vascular adverse effects and there is no residual and persistent curarization or recurarization.

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